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OSTEOPETROSIS (MARBLE BONES) IN AN INFANT

REVIEW OF THE LITERATURE AND REPORT OF A CASE

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Osteopetrosis (marble bones, *Marmorknochenkrankheit,* Albers-Schönberg's disease, osteosclerosis fragilis generalisata, *maladie des os marmoréens*) is a disease characterized essentially by increased thickness and density of the cortical and spongy portions of the entire osseous system. The marrow cavity may be encroached on to the point of obliteration, and there are frequent but less constant alterations in the external configuration of certain parts of the skeleton. Roentgenographically the individual bones appear opaque, heavy and lacking in finer structure. These changes are characteristically, although not invariably, associated with a myelophthisic type of anemia, the origin of which is closely bound up with the etiology of the osseous sclerosis. There may be other manifestations, such as multiple pathologic fractures, chronic osteomyelitis, hydrocephalus, optic atrophy and enlargement of the liver, the spleen and the lymph nodes throughout the body. The disease shows a striking familial tendency and is occasionally hereditary.

Osteopetrosis is a rare disease. Sixty-five cases have been reported in the literature, either in detail or by allusion, up to 1932. To this number may be added the case which we are about to describe. The condition deserves the attention of pediatricians. In fully half the published reports the diagnosis was made before the twelfth year of life, and it may be assumed that in many of the remaining patients the disease developed well within the pediatric age period. Notwithstanding this fact we have been unable to discover a discussion of osteopetrosis in English in a pediatric journal. Numerous reports of cases and critical dissertations have appeared in German, but the only easily available articles in English are those of Davis,[1] Alexander,[2] Karshner[3] and Pirie.[4]

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1. Davis, G. B.: Osteosclerosis Fragilis Generalisata, Arch. Surg. **5**:449 (Nov.) 1922.

(Footnotes continued on next page)

EARLY REPORTS

Diffuse sclerosis of the skeleton was first described by Hueck,[5] in 1879, as a chance finding at postmortem examination in a case of leukemia. Similar examples of leukemia or pseudoleukemia associated with quantitative and qualitative changes in the structure of bone were reported by Neumann,[6] in 1880, by von Jaksch [7] and Schwarz,[8] in 1901, and by Askanazy [9] and Schmorl,[10] in 1904. However, it remained for Albers-Schönberg, a roentgenologist of Hamburg, to show that sclerosis of the osseous system could be detected during life. His communications,[11] in 1904 and 1907, and those of Reiche,[12] in 1915 and 1929, served to delineate the clinical picture already alluded to and to segregate such cases, clinically at least, from the group in which leukemia was an outstanding feature. For a number of years the terms "Albers-Schönberg's disease" or "marble bones" were used to designate the condition. Laurell and Wallgren [13] adopted the title "osteosclerosis fragilis generalisata," and in 1926 Karshner [3] introduced the term "osteopetrosis" (stony bones) as being a single word suggesting the hardness and possibly the brittleness of the skeleton. Karshner was

2. Alexander, W. G.: Report of a Case of So-Called "Marble-Bones" with a Review of the Literature and a Translation of an Article, Am. J. Roentgenol. **10**:280, 1923.

3. Karshner, R. G.: Osteopetrosis, Am. J. Roentgenol. **16**:405, 1926.

4. Pirie, A. H.: The Development of Marble-Bones, Am. J. Roentgenol. **24**:147, 1930; Marble Bones, ibid. **30**:618, 1933.

5. Heuck, G.: Zwei Fälle von Leukämie mit eigenthümlichen Blut-respektive Knockenmarksbefund., Virchows Arch. f. path. Anat. **78**:475, 1879.

6. Neumann, E.: Ueber leukaemische Knockenaffectionen, Berl. klin. Wchnschr. **17**:281, 1880.

7. Von Jaksch, R.: Multiple Periostaffection und an myelogene Leukämie mahnender Blutbefund, Ztschr. f. Heilk. (Abt. f. inn. Med.) **22**:259, 1901; Prag. med. Wchnschr. **26**:2 and 19, 1901.

8. Schwarz, E.: Ein Fall von Leukämie mit Riesenzellenembolie und allgemeiner Osteosklerose, Ztschr. f. Heilk. (Abt. f. path. Anat.) **22**:294, 1901.

9. Askanazy, M.: Ueber extrauterine Bildung von Blutzellen in der Leber, Verhandl. d. deutsch. path. Gesellsch. **7**:58, 1904; Centralbl. d. allg. Path. u. path. Anat. **15**:535, 1904.

10. Schmorl: Leukämie mit Ausgang in Osteosklerose, München. med. Wchnschr. **51**:537, 1904.

11. Albers-Schönberg, H.: (*a*) Röntgenbilder einer seltenen Knochenerkrankung, Aertzl. Vereinald. Hamburg, Feb. 9, 1904; München. med. Wchnschr. **51**:365, 1904. (*b*) Eine bisher nicht beschriebene Allgemeinerkrankung des Skelettes im Röntgenbild, Fortschr. a. d. Geb. d. Röntgenstrahlen **11**:261, 1907.

12. Reiche, F.: (*a*) Osteosklerose und Anämie, München. med. Wchnschr. **62**:944, 1915. (*b*) Zur Kenntnis der Osteosklerosis generalisata fragilis, München. med. Wchnschr. **76**:1078, 1929.

13. Laurell, H., and Wallgren, A.: Untersuchungen über einen Fall einer eigenartigen Skeletterkrankung (Osteosclerosis fragilis generalisata), Upsala läkaref. förh. **25**:309, 1920; abstr., J. A. M. A. **76**:560 (Feb. 19) 1921.

able to collect eighteen cases, to which he added four personal observations. In his article all the previous reports were briefly summarized. We have been able to add forty-three cases to this collection, and since the number is large we have not thought it practicable to attempt a synopsis of each. The data for such a summary are lacking in several instances.

In table 1 are included all the examples of osteopetrosis which we have discovered. It has seemed worth while to attempt to give some idea of the frequency of the disease. For this reason we have included several cases which have not been reported in detail, but of the authenticity of which there is sufficient evidence to warrant their incorporation here. In this category belong the cases of Fujiki,[14] Jacquet [15] and Mayer,[16] which were vouched for by Lauterburg.[17] Péhu, Policard and Dufourt [18a] mentioned a verified but unreported case seen by Parsons and Wilkinson in Birmingham. Sear's [19] second case is represented in the literature only by the reproduction of a roentgenogram and a descriptive title in an article on osteitis fibrosa.

The Albers-Schönberg syndrome is one of a group of combined diseases of bone and of the blood-forming apparatus. The whole group was well discussed in a recent publication by Wolf.[20] Although typical examples present little difficulty in classification, there are several cases in the literature which are not capable of exact grouping. The clinical data concerning the cases of Assmann,[21] Schmidt [22] and Goodall [23] are

14. Fujiki, quoted by Lauterburg.[17b]

15. Jacquet, cited by Lauterburg.[17b]

16. Mayer, O. B., cited by Lauterburg [17b] and in personal communication to the authors (1933). Reported in detail in Mayer, O. B., and Pitts, T. A.: Osteopetrosis: Report of a Case, J. A. M. A. **101**:22 (July 1) 1933.

17. Lauterburg, W.: (*a*) Beitrag zur Kenntnis der Marmorknochenkrankheit, Schweiz. med. Wchnschr. **56**:441, 1926. (*b*) Beitrag zur Kenntnis der Osteosclerosis fragilis generalisata (Marmorknochenerkrankung Albers-Schönberg), Schweiz. med. Wchnschr. **58**:677, 1928.

18. (*a*) Péhu, M.; Policard, A., and Dufourt, A.: L'ostéopétrose ou maladie des os marmoréens, Presse méd. **39**:999, 1931. (*b*) DuPont, J.: L'ostéopétrose ou maladie des os marmoréens, Lyons, M. Audin & Company, 1930. We have been unable to obtain this article, but believe it should be listed for the convenience of readers abroad. It is the only reference cited which we have not read.

19. Sear, H. R.: M. J. Australia **2**:519, 1928, illustration (fig. 22) with legend; no report of case.

20. Wolf, C.: Ueber einen Fall von osteosklerotischer Pseudoleukämie: Beitrag zur Frage der Osteosklerosen, Beitr. z. path. Anat. u. z. allg. Path. **89**:151, 1932.

21. Assmann, H.: Beiträge zur osteosklerotischen Anämie, Beitr. z. path. Anat. u. z. allg. Path. **41**:565, 1907.

22. Schmidt, M. B.: Ueber angeborne Osteosklerose, Centralbl. f. allg. Path. u. path. Anat. **18**:817, 1907.

23. Goodall, A.: Acute Myelocythaemia Associated with Osteosclerosis and Other Unusual Features Occurring in an Infant, Edinburgh M. J. **8**:500, 1912.

TABLE 1.—*Cases of Osteopetrosis Reported or Mentioned in the Literature Up to 1933*

Case	Author	Date	Sex	Age	Data
1	Albers-Schönberg [11a]	1904	M	24 yrs.	
	Albers-Schönberg [11b]	1907			
	Reiche [12a]	1915	..	35 yrs.	
	Lorey and Reye: Fortschr. a. d. Geb. d. Röntgenstrahlen **30**: 35, 1923	1923	..	43 yrs.	
	Reiche [12b]	1929	..	49 yrs.	Partial autopsy
2	Assmann [21]	1907	?	24 hrs.	Complete autopsy; no clinical data
3	Schmidt [22]	1907	?	30 hrs.	Complete autopsy; no clinical data
	Schmidt [36]	1927			
4	Fujiki [14]	1914	?	?	
5	Sick: Ueber drei Fälle einer seltenen Skeletterkrankung, Leipzig, Leopold Voss, 1914	1914	F	15 yrs.	
	Lorey: Verhandl. d. deutsch. Röntg. Gesellsch. **11**: 56, 1921	1921			
	Lorey and Reye	1923			
6	Sick	1914	F	3½ yrs.	
	Lorey	1921			
	Lorey and Reye	1923			
7	Sick	1914	F	2½ yrs.	
	Lorey	1921			
	Lorey and Reye	1923			
8	Lorey	1921	F	3 wks.	
	Lorey and Reye	1923			
9	Laurell and Wallgren [13]	1921	M	12 yrs.	
10	Schulze: Arch. f. klin. Chir. **118**: 411, 1921	1921	M	11 yrs.	Complete autopsy
11	Davis [1]	1922	M	11 yrs.	
12	Ghormley: Bull. Johns Hopkins Hosp. **33**: 444, 1922	1922	M	8 yrs.	
13	Ghormley	1922	M	Adult	
14	Alexander [2]	1923	F	43 yrs.	
15	Lanari and Lanari: Rev. Asoc. méd. argent. **36**: 1193, 1923	1923	F	23 yrs.	
16	Clairmont and Schintz [25]	1924	F	25 yrs.	Biopsy: femur
17	Nadolny: Jahrb. f. Kinderh. **105**: 212, 1924	1924	M	4 mos.	Complete autopsy
18	Edel: Beitr. z. Anat. Physiol., Path. u. therap. Ohres **21**: 325, 1924	1924	F	14 yrs.	Biopsy: maxilla
19	Kraus and Walter [27]	1925	F	3 yrs.	Complete autopsy
20	Jacquet [15]	1925	?	?	
21	Karshner [3]	1926	F	11½ mos.	
22	Karshner [3]	1926	F	19 mos.	
23	Karshner [3]	1926	M	3½ yrs.	
24	Karshner [3]	1926	F	11 yrs.	
25	Bernhardt [26]	1926	M	26 yrs.	Biopsy: sternum
26	Lauterburg [17]	1926	M	33 yrs.	Biopsy: rib
27	Lauterburg [17]	1928	M	31 yrs.	
28	Cohn and Salinger: Med. Klin. **23**: 285, 1926	1926	F	18 yrs.	
29	Cohn and Salinger	1926	F	21 yrs.	
30	Cohn and Salinger	1926	M	20 yrs.	
31	Cohn and Salinger	1926	M	48 yrs.	
32	Sear: Brit. J. Surg. **14**: 657, 1927	1927	M	6 yrs.	
33	Marque: Semana méd. **34**: 581, 1927	1927	F	10 yrs.	
34	Marque	1927	M	12 yrs.	
35	Mayer [18]	1928	F	10 yrs.	
36	Bonta: Proc. Staff Meet., Mayo Clin. **3**: 10, 1928	1928	M	58 yrs.	
37	D'Istria: Radiol. Med. **15**:473, 1928	1928	M	30 yrs.	
38	Parkinson: M. J. Australia **2**: 284, 1928	1928	M	Adult	
39	Sear [19]	1928	F	20 yrs.	
40	Ellinger: Röntgenpraxis **1**: 816, 1929	1929	F	17 yrs.	
41	Merrill: Am. J. Roentgenol. **21**: 361, 1929	1929	M	37 yrs.	
42	Kopyloff and Runowa: Fortschr. a. d. Geb. d. Röntgenstrahlen **40**: 1042, 1929	1929	M	20 yrs.	Biopsy: scapula
43	Flood: California & West. Med. **31**: 208, 1929	1929	F	11 yrs.	
44	Alter: Arch. Path. **11**: 509 (March) 1931	1930	F	8 mos.	Complete autopsy
45	Kudrjawtzewa: Arch. f. klin. Chir. **159**: 658, 1930	1930	F	10 yrs.	Biopsy: femur
46	Kudrjawtzewa	1930	F	4 yrs.	
47	Kudrjawtzewa	1930	M	8 mos.	
48	Scharsich: Beitr. d. klin. Chir. **151**: 561, 1930	1930	M	10 yrs.	
49	Pirie [4]	1930	F	Adult	
50	Pirie	1930	M	5 yrs.	
51	Pirie	1930	F	8 yrs.	
52	Pirie	1930	F	11 yrs.	
53	Pirie	1930	F	14 yrs.	Partial autopsy
54	Llado: Rev. d. orthop. **18**: 740, 1931	1931	F	17 yrs.	
55	Windholz: Ztschr. f. Kinderh. **51**: 708, 1931	1931	?	11 mos.	
56	Priesel: Wien. klin. Wchnschr. **44**: 1065, 1931	1931	F	11 mos.	
57	Priesel	1931	F	12 mos.	

TABLE 1.—*Cases of Osteopetrosis Reported or Mentioned in the Literature Up to 1933—Continued*

Case	Author	Date	Sex	Age	Data
58	Péhu, Policard and Dufourt [18a] and Du-Pont [18b]	1931	M	27 mos.	Complete autopsy
59	Parsons and Wilkinson [18a]	1931	M	4 mos.	
60	Camauer, Burlando and Mortola: Soc. de med. int. y Soc. de tisiol. **7**: 429, 1931	1931	M	19 yrs.	
61	Licht: Hospitalstid. **74**: 50, 1931	1931	F	12 yrs.	
62	Frank: Nederl. tijdschr. v. geneesk. **75**: 5794, 1931	1931	F	6 mos.	Partial autopsy
63	Frank	1931	F	2 mos.	
64	Frank	1931	M	2 yrs.	Splenectomy
65	Gortan: Boll. e. mem. Soc. piemontese di chir. **2**: 769, 1932	1932	F	72 yrs.	

inadequate; none of the patients were studied by roentgen rays. Certain authors do not accept them as true examples of Albers-Schönberg's disease. We follow the precedent of the more eminent authorities in including them; they possess considerable historic interest. It must be emphasized that conclusions as to pathogenesis based on these cases should be made with reservation.

We regard the example of myelocythemia with changes in the bones reported by Oesterlin [24] as being outside our group. He classified it with von Jaksch's "periostitis multiplex cum myelocythaemia," but certain writers on osteopetrosis (Clairmont and Schintz,[25] Bernhardt [26] and Kraus and Walter [27]) have included it in their series.

REPORT OF A CASE

History.—Lydia G., aged 5 months, a child of Italian parents who spoke English poorly, was referred to the Babies' Hospital on Aug. 11, 1932, through the courtesy of Dr. John B. Ahouse of Yonkers, N. Y. The complaint on admission was "poor development and heavy breathing" for about three months.

The father, mother and a brother of 12 years were living and well. The parents were first cousins, the maternal grandfather and the paternal grandmother being brother and sister. There had been three other children, one girl dying at 5 years of measles, a boy dying at 4 months of "bronchitis" and a girl dying at 4 months, following the removal of adenoids. These three children were described as having been of normal appearance and not stigmatized by enlargement of the head, pallor, visual disturbances or any of the more obvious characteristics of the disease in question. There had been no abortive pregnancies, and there was no history of familial disease.

There had been a normal pregnancy, during which the mother's health was good. Labor lasted for five hours; our patient was born before the arrival

24. Oesterlin, E.: Ein Fall kombinierter Knochen-Bluterkrankung, Virchows Arch. f. path. Anat. **247**:589, 1923.

25. Clairmont, P., and Schintz, H. R.: Klinische, röntgenologische und pathologisch-anatomische Beobachtungen zur Marmorknochenerkrankung, Arch. f. klin. Chir. **132**:347, 1924.

26. Bernhardt, H.: Ein Beitrag zur Marmorknochenerkrankung (Albers-Schönberg'sche Krankheit), Klin. Wchnschr. **5**:415, 1926.

27. Kraus, E. J., and Walter, A.: Zur Kenntnis der Albers-Schönberg'schen Krankheit, Med. Klin. **21**:19, 1925.

of the obstetrician. The birth weight was 5¼ pounds (2.381 Kg.). The parents thought the infant was normal at the time of birth. She was fed at the breast, and did well for the first two months, at which age a "heavy cold" developed with difficult breathing which persisted up to the time of admission to the hospital. During the six weeks following the onset of this disturbance the infant had six or seven loose stools a day, and there was occasional vomiting. At the age of 3½ months she was taken to a hospital in another city. There it was found that she had rickets. She had received no cod liver oil up to this time. The hemoglobin content was 70 per cent, the red blood cell count, 3,700,000 and the white blood cell count, 8,200, with 73 per cent polymorphonuclears, 25 per cent small mononuclears and 2 per cent large mononuclears. She remained in the hospital for one month, and while there was given a formula

Fig. 1.—Patient L. G., who showed retardation of development; slight enlargement of the head; blindness; a rachitic rosary; enlargement of the liver, spleen and superficial lymph nodes; anemia.

of whole milk, water and dextrimaltose together with cereal and vegetables. During this time she received from 10 to 20 drops of viosterol and from 2 to 4 cc. of cod liver oil each day. On discharge from this hospital she was taken home, where she remained for ten days. During this time she refused her food and was constipated. She was then admitted to another hospital in the same city. There, a blood count showed: hemoglobin content, 48 per cent; red blood cells, 1,520,000; white blood cells, 60,000, with a differential count of polymorphonuclear leukocytes, 28 per cent; lymphocytes, 55 per cent; eosinophils, 2 per cent; basophils, 2 per cent; myelocytes, 13 per cent, and normoblasts, 34 per hundred white blood cells. There were polychromasia and basophilic stippling. Roentgenographs of the long bones and chest were interpreted as suggesting a

"general constitutional disease on the basis of either rickets or congenital syphilis or possibly a combination of the two." The Wassermann reaction of the blood was negative. The child was given a transfusion of 130 cc. of whole blood from the father, and was referred to the Babies' Hospital, a few days later, for further study.

Physical Examination.—On admission, examination revealed an extremely pale, irritable, white female infant of 5 months, who appeared younger than her age. Her weight was 4,100 Gm., length, 55 cm., circumference of the head, 41 cm., and of the chest, 34 cm., and abdominal circumference, 33 cm. The head was somewhat large, with overhanging brow and prominent frontal bosses suggesting mild hydrocephalus. The anterior fontanel was open 2 cm. in the transverse

Fig. 2.—Increased density of all the bones of the skull, particularly those of the base, and narrowing of the sella turcica.

diameter, and showed increased tension. The posterior fontanel was closed. There was well marked craniotabes. The veins of the scalp were distended. There was slight exophthalmos with a convergent squint. The vision appeared diminished, and there were coarse horizontal nystagmoid movements. The ocular tension seemed normal. The sclerae were faint bluish white. The pupils reacted sluggishly to strong light. The fundi showed optic atrophy, probably complete. There was a profuse mucoid nasal discharge. The breathing space was apparently narrowed. There were no teeth. The ear drums were moderately injected. The superior portion of the thorax was prominent, and marked costochondral beading and a Harrison's groove were seen. The respirations were noisy and of the type usually associated with nasal obstruction. The abdomen was promi-

nent, and showed dilated veins and a small umbilical hernia. The edge of the liver could be felt at the level of the umbilicus. The organ was firm but smooth. The spleen was unusually hard and extended to the iliac crest. The notch could not be felt. The ends of the long bones were visibly and palpably enlarged. The superficial lymph nodes were moderately enlarged. The deep reflexes were normal.

Laboratory Examination.—The initial blood count showed a 79 per cent hemoglobin content and 4,390,000 red cells (the child had received a large transfusion a few days before). The white cell count was 20,000, with 57 per cent of granular and 43 per cent of nongranular cells. The blood platelets numbered 104,000. The technic of counting which we employ gives normal values between 300,000

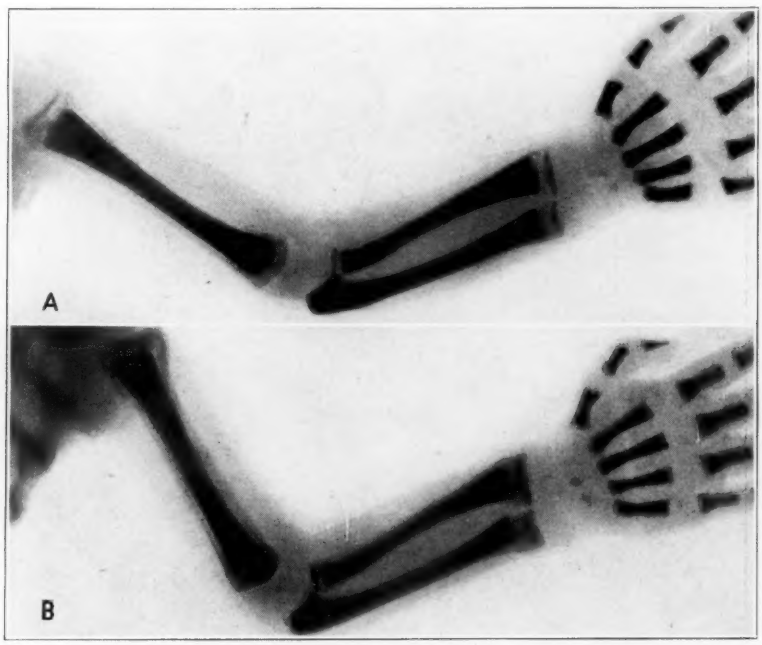

Fig. 3.—*A*, an arm (August 13) showing increased opacity of the bones, with obliteration of the medullary cavity and cortical markings; bands of osteoid at the ends of the shafts beneath the reformed zones of primary calcification in healing rickets, and the thin cloak of partially calcified osteoid under the periosteum. *B*, the same arm (September 28) showing the deposition of calcium in the metaphyseal bands and under the periosteum, demonstrating the extent of healing of rickets in forty-six days.

and 700,000. The bleeding time was three and one-half minutes and the clotting time seven and one-half minutes. The urine was normal save for a trace of albumin and a few red cells. The blood chemistry values were normal with the exception of a slight reduction in both serum calcium and serum phosphorus. The van den Bergh test gave an indirect positive result, and the bilirubin was 0.41 mg. per hundred cubic centimeters. The Kahn precipitation test of the blood serum gave negative results.

A lumbar puncture shortly after admission showed a pressure of 520 mm. of water. The child was not struggling at the time of the reading. The fluid was clear and colorless at first, but became bloody through trauma, so no further tests were performed.

On admission the diagnoses suggested were: pachymeningitis interna haemorrhagica, scurvy, rickets, developmental defect, Cooley's anemia and leukemia. As is generally true in these cases, the correct diagnosis was established by roentgenographic examination.

Roentgen Examination.—On August 13, roentgenograms of the skeleton showed a markedly increased homogeneous density of the whole skeleton as compared with a normal child of the same age. In the long bones there was complete obliteration of the shadow of the medullary canal and of the trabecular markings.

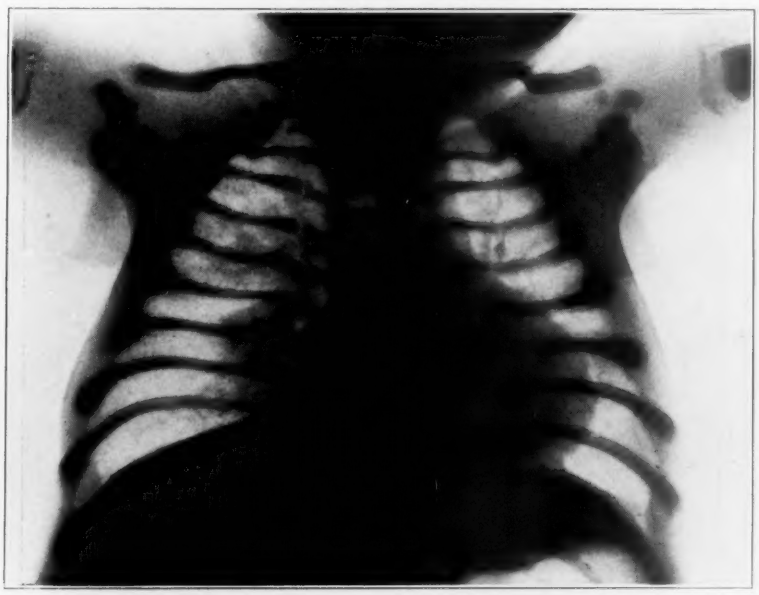

Fig. 4.—The chest, showing sclerosis of the ribs, vertebrae and clavicles.

In the skull the changes were particularly well marked at the base. The sella turcica was small, and the body of the sphenoid bone was very dense. All the phalanges were involved. In certain films of the humeri the nutrient canal was indefinitely outlined, and in some of the films the radii, ulnas and tibias showed a faint suggestion of irregular longitudinal striation. There were no alternating bands of greater and lesser density across the shafts of the bones.

Peripheral to the margins of the humeri, radii, ulnas, scapulas, tibias fibulas, femurs, ribs, first metacarpal bones and bones of the pelvis was a thin white line following closely the contour of the bones. It could not be seen about the vertebral bodies or the phalanges. In the cylindric bones it terminated at the epiphyseodiaphyseal junction, where it joined a similar line extending transversely across the bones. In this fashion a "frame" or "cloak" was produced which enclosed the diaphyseal portion of the bones. Across the ends of the shafts of the

long and short hollow bones, limited laterally and toward the epiphyses by the lines just described, was a bandlike zone showing generally decreased density. This zone was about 1 cm. wide in the longer bones and a few millimeters wide in the shorter ones. It contained numerous irregularly arranged flecks of calcium density. In the tibias these shadows had a somewhat longitudinal arrangement.

Two minute centers of ossification were present in each carpus, probably representing the capitate and hamate bones, respectively. The centers of ossification of the proximal and distal epiphyses of the humerus and of the proximal epiphyses of the femurs were faintly visible. The centers of ossification of the

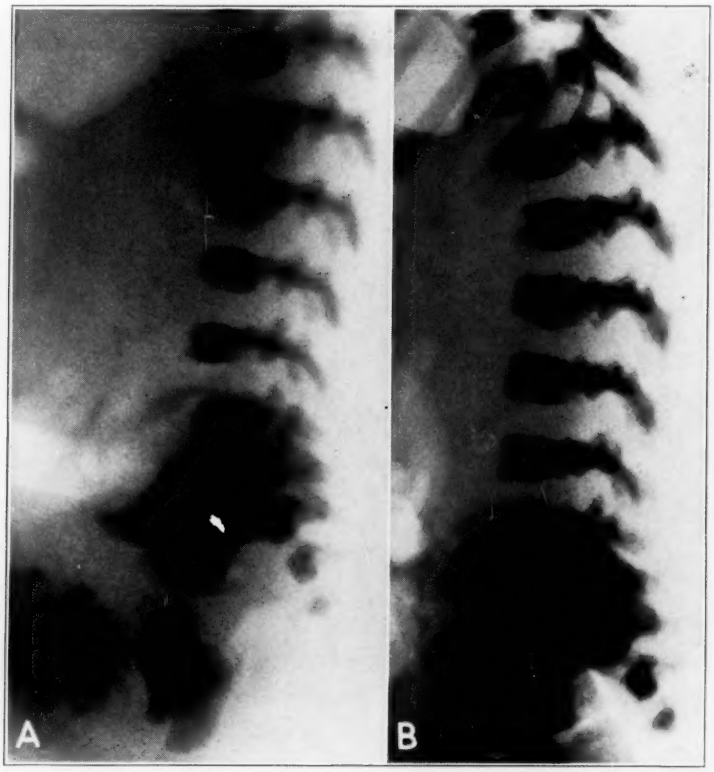

Fig. 5.—*A,* the lumbar portion of the spine (August 13) showing sclerosis of the vertebrae and bones of pelvis, and a cloak of osteoid just visible around the bones of the pelvis. *B,* the lumbar portion of the spine (September 28) showing the deposition of calcium in osteoid about the vertebrae and bones of the pelvis.

proximal epiphyses of the tibias were well developed, and those of the cuboids were present. All the centers mentioned appeared moth-eaten and of approximately the same density as the metaphyseal bands already alluded to.

The centers of ossification in the distal epiphyses of the femurs and those in each os calcis and astragalus were also present. Their appearance was different from that of the other centers of ossification. They presented a central nucleus of increased density corresponding in degree of opacity with the shafts of the long

bones already described. Surrounding this nucleus was a zone of relatively decreased density analogous to the bands of lesser opacity across the ends of the shafts. This, in turn, was bounded by a thin line which encircled the center of ossification. This boundary line was seen best in the os calcis and in the astragalus, and less well in the centers of ossification of the femurs.

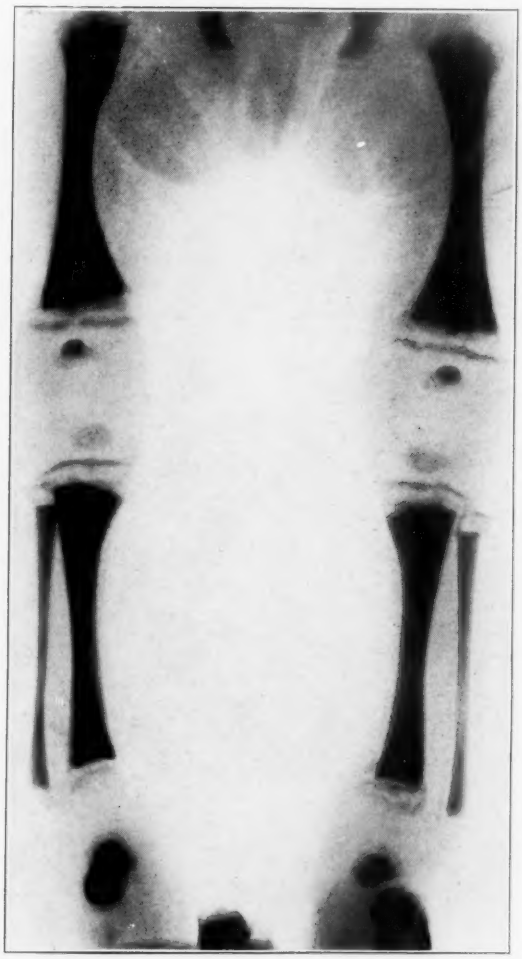

Fig. 6.—The lower extremities (August 13) showing the centers of ossification of varying density owing to the differences in the time of their appearance. Infractions of both ends of fibulas are present.

The length and diameter of the bones were definitely less than those of a normal child used as a control.

At each end of the fibulas and at the distal ends of the ulnas there was a slight but definite angulation between the more opaque diaphyseal portion of the bones and the less dense metaphyseal zone. The point of angulation was located

precisely at the sharp transition between the two types of shadow. In the anteroposterior exposures there was no evidence of separation of the proximal and distal portions. Angulation was probably present at the vertebral ends of the lowest two ribs on each side.

The general contour of the bones was well preserved. There was no clubbing or cyst formation. The cranial sutures were visible, and there was no suggestion

Fig. 7.—The lower extremities (September 28) showing the features observed in figure 6 intensified through the deposition of calcium in the osteoid.

of premature synosteosis. The maxillary sinuses were present but small. No deposits of calcium were seen in the soft tissues.

Interpretation: The diffuse increase in the density of the bones, with obliteration of the shadow of the marrow cavity and loss of the finer markings of bone structure, is characteristic of osteopetrosis.

The condensing changes described involve all bones and all centers of ossification which were laid down during intra-uterine life. This is exemplified by the involvement of the central portion of the diaphyses of the humeri, radii, ulnas, femurs, tibias and fibulas. The primitive center of ossification for the shafts of these bones appears at about the eighth week of fetal life. The central portions of the nuclei of ossification of the os calcis, of the astragalus and of the distal epiphyses of the femurs show the same degree of increase in density (the center of ossification of the os calcis appears in the sixth fetal month, of the astragalus in the eighth fetal month and of the distal epiphysis of the femur at about the time of birth). As seen roentgenologically, the diameters of the dense central nuclei of the os calcis and of the astragalus are greater than those of the two distal epiphyses of the femurs.

These findings indicate that the disease began in utero and was probably present by the eighth week of fetal life.

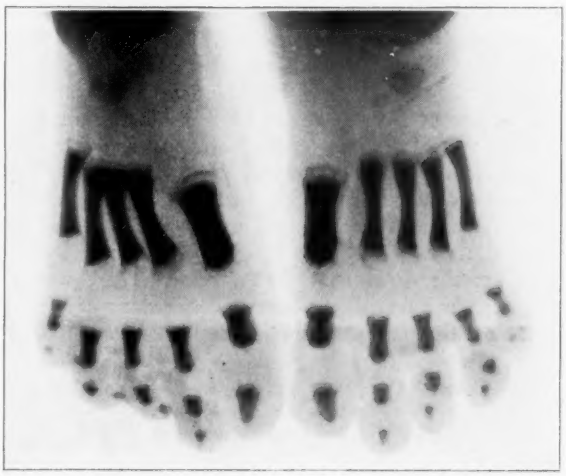

Fig. 8.—The feet (September 13) showing the same features as those found in the rest of the skeleton.

In the centers of ossification which appear "at time of birth," or thereafter, this increase in density is present only in a central nucleus or is lacking completely. In this group fall the capitate and hamate bones of the carpus (which appear in the latter half of first year), the distal and proximal centers of the humerus (which appear at birth and during the first year respectively), the proximal centers of the femurs (which appear during the first year), the proximal centers of the tibias (which appear at birth) and the cuboids (which appear at birth). These findings suggest that some marked alteration in the original pathologic process took place at or about the time of birth. The suspicion finds added confirmation in the presence of bands of decreased density in the ends of the shafts and in the annular areas of decreased density surrounding the central, more opaque, nuclei in the os calcis, in the astragalus and in the distal ends of the femurs.

The "cloaks" enclosing the long bones and the zones of decreased density are compatible with rickets. The thin lines surrounding the bones and the line located

at the epiphyseodiaphyseal juncture represent the stage of early healing. The sharp line surrounding certain of the centers of ossification has the same significance.

Impression: It appeared that we were dealing with a typical case of marble bones, the onset of which could be dated back as far as the eighth week of fetal life. At some period close to the time of birth the process was complicated by superadded rickets. After that the bones continued to grow in length and diameter, but the accretion consisted largely of osteoid. At some recent time the rickets had begun to heal, for there was evidence of deposition of calcium in the epiphyseodiaphyseal juncture (primary zone of ossification), under the periosteum of the long bones and about the periphery of some of the centers of ossification. There was probable infraction of both ends of the fibulas, the distal ends of the ulnas and the vertebral ends of the two ribs lowest on both sides.

On August 28, the general features were as described before. There had been a marked increase in the density of the rarefied bands in the metaphyses. The linear shadows bounding the long bones had become thicker and more opaque. Nearly every bone gave the impression of being embedded in a matrix of moderately opaque material which was, however, less dense than the bones themselves. The appearance of the femurs was not unlike that of the calcified hematomas seen in healing scurvy, but all other findings contradicted this possibility. Beading at the costochondral junctures was more readily visible than before. Many of the centers of ossification which were formerly only faint flecks now appeared in their full outline, although their density was still much less than that of the more opaque portions of the skeleton. There was a definite infraction at the vertebral ends of the tenth rib on the right and of the tenth and eleventh ribs on the left, and there was infraction with angulation at both ends of the fibulas and at the distal ends of the ulnas. There was apparently no interruption of the continuity of the periosteum. The cloak of what was assumed to be calcifying osteoid tissue was now clearly seen surrounding the bodies of the vertebrae.

Roentgenograms showed the tooth-buds in normal position and of normal appearance.

Roentgenograms of the hands of the father, mother and elder brother showed nothing abnormal. The medullary canals were well visualized and the finer markings were seen clearly.

Blood Studies.—Numerous hematologic examinations were performed the results of which are incorporated in table 2.

Dr. Martha Wollstein made the following note concerning the findings: The patient was admitted shortly after a large transfusion had been given, and the first blood count showed 4,390,000 red blood cells per cubic millimeter. The number of red cells diminished steadily, so that there were only 967,000 per cubic millimeter three months after admission. The hemoglobin content fell from 79 per cent (13.4 Gm.) to 20 per cent (3.4 Gm.). The drop in the content of red cells and hemoglobin was most rapid during the last month of life. The number of blood platelets also diminished steadily, from 104,000 per cubic millimeter on admission to 12,000 ten days before death. The leukocyte count remained between 20,000 and 40,000, once reaching 51,000. However, in the final two weeks before death there were only between 13,090 and 16,850 white cells per cubic millimeter. The number of lymphocytes increased as the number of polymorphonuclear leukocytes diminished, but during the final month there was a rise in the number of polymorphonuclear cells, with an increase in young marrow forms, both red and white. The hematologic picture was that of panmyelophthisis, with every marrow

element involved. The final developments were suggestive of myeloid leukemia, in the character of the cells rather than in the number present.

Blood Chemistry.—The only consistently abnormal feature was the uniform lowering of the serum phosphorus concentration. This was compatible with the

TABLE 2.—*Hematologic Observations During the Period in the Hospital*

Date	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells	Platelets	Polymorphonuclears, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Eosinophils, per Cent	Reticuloeytes, per Cent	Basophils, per Cent	Myelocytes, per Cent	Nucleated Red Blood Cells, per C.Mm.
8/11	79	4,390,000	20,708	.....	43	35	12	2	....	2	6	3,510
8/12*	80	4,344,000	28,600	104,000	46	37	4	2	8.04	..	9	1,710
8/18†	68	3,336,000	27,750	66,000	39	50	2	1	4.6	..	7	1,800
8/24	60	3,050,000	27,000	100,000	33	57	4	..	....	..	6	4,050
8/26	70	4,070,000	29,350	.....	37	52	2	..	....	..	5	3,810
8/27	65	3,541,000	24,414	.....	24	65	..	..	....	..	3	2,686
8/30	73	3,650,000	33,900	.....	31	58	..	2	....	3	5	4,750
9/ 2	67	3,790,000	38,800	.....	52	40	1	1	....	..	6	5,430
9/ 6	65	3,660,000	25,900	50,000	41	54	1	1	....	..	3	7,770
9/ 9	70	3,180,000	20,700	.....	44	45	4	2	....	2	5	3,730
9/13	67	3,350,000	40,000	40,000	27	66	3	2	....	1	4	6,000
9/15	62	2,980,000	51,700	40,000	44	44	..	13	....	1	10	7,700
9/20	63	3,200,000	32,600	30,000	58	30	..	..	....	2	10	5,520
9/26	52	2,264,000	41,344	30,000	45	26	..	2	8.7	1	13	7,840
9/26	Transfusion of 80 cc. of whole blood											
9/29	74	3,520,000	23,800	52,000	52	36	6	..	7.9	2	4	2,170
10/ 4	60	3,004,000	20,250	36,000	33	66	..	..	....	..	..	2,020
10/10	50	2,480,000	19,440	46,000	25	67	3	1	9.3	..	4	
10/20	45	2,016,000	32,800	20,000	27	62	..	..	....	..	9	7,540
10/21	Transfusion of 90 cc. of whole blood											
10/22	62	2,376,000	39,600	28,000	40	47	3	4	....	..	5	
11/ 5	29	1,088,000	15,300	36,000	58	28	1	1	....	..	10	910
11/10	20	848,000	13,000	.....	54	36	1	..	....	..	24	3,125
11/17	20	967,000	16,850	.....	58	35	1	..	....	..	3	840

* Coagulation time 7½ minutes. Bleeding time 3½ minutes.
† Bleeding time 3 minutes; perioxidase stain, 53 per cent granular, 47 per cent nongranular.

TABLE 3.—*Blood Chemistry in the Case Reported by McCune and Bradley*

	8/12	8/18	9/2	10/1	10/24	10/25, 10/26, 10/27	10/31
Whole blood							
Nonprotein nitrogen, mg.*	36.3	27.6	...	...	31.2	Parathyroid	29.6
Chlorides, mg.	524.0	554.0	...	...	515.0	extract,	548.0
Sugar, mg.	.....	117.0	...	...	120.0	10 units	114.0
Serum						intramus-	
Calcium, mg.	9.4	9.6	9.2	8.0	10.0	cularly	9.2
Phosphorus, mg.	3.8	3.5	3.6	3.6	3.7		3.4
van den Bergh	Indirect trace	Indirect trace					
Bilirubin, mg.	0.41	Trace					
Plasma							
Albumin, Gm.	3.8	.....	...	...	.....	.....	4.63
Globulin, Gm.	2.16	.....	...	...	.....	.....	3.02
Fibrinogen, Gm.	0.20						
Carbon dioxide, vol. per cent	44.0						

* Per hundred cubic centimeters.

presence of rickets. The serum calcium reached the low level of 8 mg. per hundred cubic centimeters on one determination. During the rest of the time it was only slightly below the normal value.

The child was subjected to a metabolic study of the calcium and phosphorus balance. This will be discussed under a special heading.

Course.—The clinical course was progressively downhill. It was characterized by persistent nasopharyngeal infection and brief intercurrent otitis media. Her

weight remained practically stationary until the time of death. Epistaxis was noted on two occasions. At this time the blood platelets numbered more than 40,000. Five weeks after admission petechiae appeared over the abdomen and on the arms, legs and neck. The number of platelets had fallen to 30,000. Transfusion on two occasions (80 and 90 cc.) had no significant effect.

The child died fifteen weeks after admission, in the course of a relatively mild infection of the upper respiratory tract. The terminal period was characterized by hypothermia in place of fever. Although a few spasmodic movements of the face had been noted from time to time, there had been no frank convulsions. There was no clinical evidence of pneumonia. Blood cultures were not taken. Permission for an autopsy was not obtained.

PATHOLOGY: MORPHOLOGIC INVESTIGATIONS

The pathologic data on which attempts to elucidate the anatomic changes in osteopetrosis are based come from the following sources.

Complete autopsies: Assmann: [21] no clinical data; 1 day old
Schmidt: [22] no clinical data; 30 hours
Goodall: [23] case not universally accepted; 10 weeks
Nadolny: [28] 4 months
Alter: [29] 8½ months
Péhu, Policard and Dufourt [18a] and DuPont [18b]: 27 months
Kraus and Walter: [27] 3 years
Schulze: [30] 11 years

Partial Autopsies: Frank: [31] spleen, liver, thymus gland and kidneys; 2 months
Lorey and Reye: [32] head; 7 years
Pirie: [4] knee joint, femur, tibia and fibula; 14 years
Reiche: [12b] chest and abdomen; 49 years

Biopsies: Frank: [31] splenectomy; 2 years
Kudrjawtzewa: [33] neck of femur; 10 years
Edel: [34] fragment of jaw; 14 years
Kopyloff and Runowa: [35] scapula; 20 years
Clairmont and Schintz: [25] middle of femur; 25 years
Bernhardt: [26] sternal puncture; 26 years
Lauterburg: [17] rib; 33 years

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28. Nadolny, G.: Diffuse Osteosklerose im Kindesalter, Jahrb. f. Kinderh. **105**:212, 1924.

29. Alter, N. M.; Pease, M. C., and DeSanctis, A. G.: Albers-Schönberg's Disease; "Marble-Bones," Arch. Path. **11**:509 (March) 1931.

30. Schulze, F.: Das Wesen des Krankheitsbildes der „Marmorknochen (Albers-Schönberg)," Arch. f. klin. Chir. **118**:411, 1921.

31. Frank, E. S.: Marmerbeenziekte (Osteopetrosis), Nederl. tijdschr. v. geneesk. **75**:5794, 1931.

32. Lorey and Reye: Ueber Marmorknochen (Albers-Schönberg'sche Krankheit), Fortschr. a. d. Geb. d. Röntgenstrahlen **30**:35, 1923.

33. Kudrjawtzewa, N.: Ueber Marmorknochenkrankheit, Arch. f. klin. Chir. **159**:658, 1930.

34. Edel, W.: Albers-Schönberg'sche Krankheit und Osteomyelitis des Oberkiefers, Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres. **21**:325, 1924.

35. Kopyloff, M. B., and Runowa, M. F.: Ein Beitrag zur Kenntnis der Marmorknochenkrankheit, Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:1042, 1929.

Of the eight complete autopsies listed, five were performed in cases in which the diagnosis was accurately verified during life. Most authors accept Assmann's case. The objections to its inclusion have already been stated. Goodall's case was almost identical from a pathologic point of view. The case of M. B. Schmidt [22] has been accepted generally as an example of the infantile form of Albers-Schönberg's disease, although Schmidt, in commenting on the case several years after its publication,[36] cast some doubt on its authenticity. The data from these three cases are utilized in this discussion, although it is realized that they do not constitute ideal material. The four partial autopsies and the seven biopsies were performed in well authenticated cases. The pathologic material, then, consists of observations on sixteen certain and three uncertain cases.

We present a synopsis of the most important observations, as given by the various authors. In many instances the complexity of the descriptions makes it impossible to summarize them within the limits of the available space.

ASSMANN.[21]—*Infant, 1 day old; sex not given; no clinical data; complete autopsy.*

The calvarium, ribs, vertebrae, femur, radius and ulna were examined. The compacta was thickened, the spongiosa was composed of fine meshes and the marrow was bright red. The costochondral junctures were somewhat wide but straight and the calvarium was universally thickened. There was definite new formation of bone, characterized by an increase in the number and a thickening of the trabeculae of the spongiosa. In some places the trabeculae were surrounded by osteoblasts. Certain regressive changes were found, particularly under the periosteum, but occasionally deeper in the bone. This regression was characterized by the presence of osteoclasts and sometimes by irregularly arranged and generally acellular bone lacunae. When present, the marrow spaces contained normal-looking hematogenic tissue. There was no evidence of extramedullary hematopoiesis.

SCHMIDT.[22]—*Infant, 30 hours old; sex not given; no clinical data; complete autopsy.*

There were thickening of all the spongy bone, moderate thickening of the diaphysis and sclerosis of the vertebral bodies with narrowing of the marrow cavities. The residual marrow was of normal structure without fibrosis. The vessels of the bone showed marked increase in the number of their branches. The hypophysis was enlarged and the thyroid gland showed a slight increase in size. There was some evidence of the formation of blood in the lymphoid apparatus.

GOODALL.[28]—*Female infant, 10 weeks old; clinically, anemia, jaundice, enlargement of the liver and spleen; no general glandular enlargement; no evidence of rickets or syphilis; red blood cells, 1,100,000; hemoglobin, 22 per cent; white blood cells, 75,000; polymorphonuclears, 26 per cent; lymphocytes, 14 per cent; myeloblasts, 50 per cent; normoblasts, 48,008 per cubic millimeter; no roentgenograms; complete autopsy.*

36. Schmidt, M. B.: Ueber osteosclerotische Anämie und Albers-Schönberg'sche Krankheit, Beitr. z. path. Anat. u. z. allg. Path. **77**:158, 1927.

The bones were dense, with an increase in the cancellous tissue and little marrow. The trabeculae were thickened, and the medullary cavity was obliterated. What marrow remained was hyperplastic and showed many multinucleated red cells. Microscopically, the liver, spleen and lymph glands showed infiltration with "leukemic" cells and a moderate number of nucleated red cells with a few "giant cells." There was some hemosiderosis. No detailed microscopic study of the architecture of the bones was made.

NADOLNY.[28]—*Male infant, 4 months old; typical roentgenographic picture save for the epiphyseal portions which "suggested the Trümmerfeld zone of scurvy;" complete autopsy.*

The bones were dense and hard to cut; the thickened trabeculae showed borders of osteoblasts and little osteoid; the marrow cavity and diploic spaces were obliterated, and Howship's lacunae and osteoclasts were rare. The long bones showed a thickened compacta with narrowed haversian canals; the epiphyseal line was somewhat jagged. A striking feature was the irregular destruction of cartilage and marked calcification of the cartilaginous ground-substance, with islands of calcified cartilage persisting between the primitive trabeculae. The marrow was fibrous, but contained relatively numerous myelocytes. The periosteum was inactive. There was a marked rachitic rosary resulting from infraction of all the ribs at the costochondral articulations, with a slight inward displacement of the sternal fragments and some hemorrhage at these points. Myeloid metaplasia was seen in the liver, spleen and lymph nodes. The endocrine glands were normal.

ALTER.[29]—*Female infant, 8 months old; typical, well developed case; complete autopsy.*

The bones were hard, with a thickened cortex and trabeculae; the periosteum was uneven and the line of ossification irregular. There were calcified areas in the epiphyseal cartilage, and subperiosteal hemorrhage had occurred throughout all the bones. Histologically there was no resemblance to normal bone structure; there was no definite canal system with characteristic lamellations; the haversian system was distorted, consisting of an osteoid matrix enclosing irregularly demarcated spaces filled with fibrous marrow; there was an absence of the usual layer of osteoblasts, and numerous giant cells not unlike osteoclasts were present. The most striking features were: the lack of osteoblasts; the imperfect osteogensis with lack of lamellation and the excessive calcification of the osteoid tissue. There was no extramedullary hematopoiesis.

PÉHU, POLICARD and DUFOURT.[18a]—*Male infant, 27 months old; clinically, a typical case; complete autopsy.*

There was thickening of the cortex and trabeculae. An adenoma of the parathyroid glands was found and calcium masses in the pelvis of each kidney. The histologic features were not described in the article to which we have access.[18a]

KRAUS and WALTER.[27]—*Female infant, 3 years old; typical case; complete autopsy.*

There was thickening of the trabeculae and cortex. Microscopically, much osteoid was evident; the typical osteoblasts were replaced by long, spindle-shaped, flat cells. There were numerous osteoclasts. Myeloid marrow was strikingly absent; instead there was much fibrous marrow, in some places undergoing metaplastic development into osteoid. The epiphyses were normal. There was evidence of myeloid activity in the liver, spleen and lymph nodes. The endocrine glands, including the parathyroids, were normal.

SCHULZE.[30]—*Male infant, 11 years old; atypical in the presence of the calcification of subcutaneous connective tissue; complete autopsy.*

The bones were hard and white, and no marrow was visible macroscopically. There was some irregularity of the epiphyseal line, with islands of calcification in the epiphyseal cartilage and areas of calcified cartilage in the marrow cavity. A sluggish type of endosteal and periosteal bone production was observed, with resorption decreased, a deficiency in the number of osteoclasts and little or no osteoid. The general picture was that of indolent production of bone, with sclerosis resulting from a lack of proportionate resorption. There were regressive changes in the upper end of the tibia corresponding to roentgenographic osteoporosis in this region. No note was made of the state of the extramedullary hematopoietic apparatus. Numerous deposits of calcium were seen in the soft tissues about the joints, in the blood vessels and in the trachea. No mention was made of the kidneys. The parathyroid glands were grossly and microscopically normal.

FRANK.[31]—*Female infant, 3 months old; diagnosis made in retrospect because of the subsequent occurrence of similar illness in the same family; partial autopsy.*

The thymus gland and kidneys were normal; the liver contained a trace of iron. The spleen showed changes which had at first been thought to be typical of hemolytic anemia, an opinion which was reversed on subsequent examination. Apparently there was no extramedullary hematopoiesis.

LOREY and REYE.[32]—*Girl, 7 years old; typical case; head alone examined.*

There was thickening of the skull, with narrowing of the foramina, hydrocephalus and pachymeningitis interna haemorrhagica.

PIRIE.[4]—*Girl, 14 years old; roentgenographic findings limited but typical; autopsy limited to parts of tibia, fibula and femur about the knee joint.*

There was thickening of the cortex and trabeculae, with sclerosis most marked toward the epiphyses, fading out into normal bone toward the shaft. The trabeculae were arranged in longitudinal columns, and the epiphyseal centers of ossification were relatively normal, containing hemorrhagic myeloid marrow with considerable fibrous tissue in its meshes. The diaphyses appeared to consist of calcified cartilage containing irregular open spaces and small, spherical foci of ossification. The open spaces contained fibrous marrow, with flattened osteoblasts conspicuous about the margins of these spaces. Typical osteoclasts were lacking, although there was a relatively large amount of osteoid.

REICHE.[12b]—*Man, 49 years old; Albers-Schönberg's original case; autopsy of chest and abdomen; sternum and ribs examined.*

The bones were compact, homogeneous and finely meshed, with no marrow cavity. There was no note on the microscopic appearance of the bone. There was fibrosis of the myocardium. The structure of the liver, spleen and lymph nodes was well preserved, with some increase in the fibrous tissue. Minute islands of hematopoiesis were seen in all these organs. There was some phagocytosis of the red cells with hemosiderosis.

FRANK.[31]—*Male infant, 3 months old at time of splenectomy; typical case.*

The spleen was large, but otherwise not remarkable; it was a rather cellular organ, but contained only a few red blood cells and showed no active hematopoiesis. There was no iron pigment. It was thought not to be typical of hemolytic anemia.

KUDRJAWTZEWA.[33]—*Girl, 10 years old; typical case; roentgenogram of the neck of the femur showed osteoporosis at the site of an old fracture; biopsy specimen from this region.*

The bone was somewhat crumbling. Widened haversian canals were filled with fibrous tissue, blood vessels and numerous giant cells (osteoclasts), and between the strands of fibrous tissue were some normal marrow elements. Endosteum and osteoblasts were lacking. The resorption of bone was the predominating feature.

EDEL.[34]—*Girl, 14 years old; typical case; fragment of upper jaw removed during operation for osteomyelitis.*

The density of the bone was increased; the marrow spaces were small and contained a fibrous type of marrow; flat osteoblasts were present in an average number, and many Howship's lacunae, but few osteoclasts. There was some inflammatory infiltration. The paranasal accessory sinuses were absent.

KOPYLOFF and RUNOWA.[35]—*Man, 20 years old; typical case; biopsy specimen of scapula.*

The bone was dense, with a definite haversian system; the marrow spaces were narrow and contained either myeloid marrow or fibrous tissue; there was some lacunar resorption through osteoclastic activity, and osteoblasts and newly formed bone were present.

CLAIRMONT and SCHINTZ.[25]—*Woman, 25 years old; typical case; open reduction of a fracture of the middle third of the femur; biopsy material taken at operation.*

There was massive increase in the thickness of the cortex. The microscopic architecture was completely normal save for the increased branching of the haversian canals and the blood vessels contained therein. There were numerous osteoblasts and osteoclasts.

BERNHARDT.[26]—*Man, 26 years old; typical case; sternal puncture and biopsy specimen of lymph gland.*

The bone was like ivory, without a trace of the marrow cavity. The gland showed myeloid metaplasia.

LAUTERBURG.[17]—*Man, 33 years old; typical case; biopsy specimen of rib.*

The cortex and spongiosa were not distinguishable from each other; the whole bone resembled compacta. A moderate number of osteoblasts were seen, but osteoclasts were almost completely absent, although there was some osteoid. The marrow spaces were narrow meshed, and the marrow was partly fibrous and in places undergoing metaplasia into osteoid. A small quantity of myeloid marrow was evident, and the haversian system was present, but irregularly lamellated.

Comment.—These pathologic data are arranged synoptically in the following paragraphs. For purposes of clarity we have also introduced a few of the relevant clinical and roentgenographic findings.

1. Generalized increase in the density of the cortex and the spongiosa of the bones is a constant and characteristic feature. In the spongiosa this increase results from augmentation of the number and thickness of the individual trabeculae. In the cortex the number of lamellae per unit of volume is greater than normal. In both places the increase in osseous tissue is brought about at the expense of the space usually occupied by myeloid tissue, fatty marrow and blood vessels. The spongiosa may reach a degree of density which makes it grossly indistinguishable from compact bone, so that there is no macroscopic distinction between the cortex and spongiosa.

2. The architectural pattern resulting from these changes is frequently disorderly and irregular, showing striking qualitative as well as quantitative changes from the structure of normal bone.

3. As a corollary, there is marked reduction in the number and size or complete obliteration of the intertrabecular spaces, the marrow cavity and the haversian canals.

4. The marrow spaces which remain are usually filled with fibrous tissue enclosing in its meshes small but varying quantities of active hematogenic elements. In the cases of Assmann,[21] Schmidt [22] and Goodall [23] the marrow was decreased in quantity but was qualitatively unaltered.

5. The disturbances responsible for the sclerosis seem to be located largely in the endosteal and endochondral metabolism of bone. The thickening of the cortex and of the individual trabeculae results from the laying down of both lamellated and nonlamellated bone through the activity of osteoblasts. In some cases the osteoblasts are morphologically typical, in others they have been described as distinctly abnormal. Some authors comment on their excessive number. The metaplastic formation of osteoid from fibrous tissue has been described. As the result of factors which are poorly understood, osteoid is sometimes present in an unusually large amount, ordinarily around the edges of the trabeculae. Hypothetically, one of these factors might be an intake or utilization of calcium and phosphorus insufficient to supply the demands of increased production of bone. The osteoid may be an expression of trabecular resorption similar in appearance to that seen in rickets or in osteomalacia.

Histologic observations differ considerably in respect to the presence of osteoclasts and their number. Some authors emphasize their absence while others state that they are present in normal quantity. One is almost forced to conclude, *a posteriori,* that there must be some deficiency in either their number or their activity. In two cases the lacunar resorption reached a stage amounting to osteoporosis (Kudrjawtzewa [33] and Schulze [30]).

6. Disturbances in endochondral formation of bone have been demonstrated histologically by Pirie,[4] Nadolny,[28] Alter [29] and Schulze.[30] These alterations consisted in hypercalcification of the cartilaginous ground-substance and the persistence of foci of calcified cartilage in the zone of newly formed trabeculae. Clublike widening of the ends of the shafts has been demonstrated roentgenographically in so many cases that it constitutes a characteristic feature. The rate of the longitudinal growth of bone is frequently retarded. Both facts point to irregularities in the formation of endochondral bone.

One of the characteristic roentgenographic aspects of the disease is the presence of alternating bands of greater and less density arranged parallel to the epiphyseal line. The explanation of these bands appears to lie in the relative intensity or vigor of the following factors: the

rate of longitudinal growth resulting from endochondral activity; the intensity of the osteoblastic production of bone, and the amount of osteoclastic or trabecular resorption. The bands demonstrate that the disease is relatively intermittent, and that it undergoes fluctuations in intensity, at least as far as the bones are concerned. Whether the pathologic changes in the hematopoietic apparatus are also subject to exacerbations and remissions cannot be stated with certainty. The contradictory findings at autopsy suggest this in some measure. From the data at hand we are unable to form an opinion as to whether these alternations in severity are produced by exogenous factors or whether they are entirely endogenous.

7. Pathologic changes in the periosteum are not the rule, although Alter [29] observed hemorrhage in this region. Windholz,[37] Kudrjawtzewa,[33] Priesel [38] and Frank [31] found roentgenographic evidence of periosteal thickening. Growth in diameter is only slightly retarded.

8. In general, the changes in the epiphyses are the same as those in the shafts. The centers of ossification appear at the usual time. Union of the epiphyses with the shafts was subject to delay in the cases of Laurell and Wallgren [13] and Bernhardt.[26]

9. Roentgenographic evidence of rickets may be present (Karshner,[8] Kudrjawtzewa,[33] McCune and Bradley). This observation has been made only in infants, and can hardly be taken to signify a predisposition to rickets, although our own case suggested this possibility.

10. The state of the extramedullary hematopoietic apparatus varies considerably. Reiche [12b] was surprised to find only trivial evidence of the formation of blood in the enlarged liver, spleen and lymph nodes of his patient. Alter,[29] Assmann [21] and Frank [31] found no evidence of hematopoiesis in these organs. On the other hand, M. B. Schmidt,[22] Kraus and Walter,[27] Nadolny,[28] Goodall [23] and Bernhardt [26] described varying degrees of hematogenic activity in the extramedullary apparatus in their patients. Some authors have commented on the striking quantity of inactive fibrous tissue in the lymphoid system. From this fact they have drawn the conclusion that the disturbance in hematopoiesis is one of the primary features of the disease.

11. The endocrine glands have been normal in most cases in which they were examined. However, Péhu, Policard and Dufourt [18a] found an adenoma of the parathyroid glands and associated concretions in the pelvis of each kidney. Alter [29] thought that the thyroid, thymus and pituitary glands were small. Schmidt's [22] patient had a large hypophysis

37. Windholz, F.: Osteosclerosis fragilis generalisata (Marmorknochenkrankheit) mit periostaler Knochenneubildung, Ztschr. f. Kinderh. **51**:708, 1931.

38. Priesel: Wien. klin. Wchnschr. **44**:1065, 1931.

and a slightly enlarged thyroid gland. Schulze [30] found extensive calcifications in the soft tissues and elsewhere. The parathyroid glands were normal in his patient and in those of Nadolny [28] and Alter.[29] Frank found a normal thymus.

12. Lorey and Reye [32] observed hydrocephalus with pachymeningitis. Kraus and Walter's [27] patient showed hemorrhage and thickening in the dura mater.

13. Interesting information may be culled from the reports of surgeons who have performed operations on the bones of patients with osteopetrosis. In the cases of Clairmont and Schintz,[25] Alexander,[2] Lauterburg [17b] and Parkinson,[39] the bones were extraordinarily hard and unusual effort was required to cut through them. Other authors have concurred in this testimony. Pirie,[4] however, found that the bones were more easily penetrated by a drill than was a piece of normal bone which he used as a control. From this experience he felt that the consistency of the bones more closely approximated that of chalk than that of marble. Accordingly he proposed the term "chalky bones" in place of "marble bones." As will appear in the following section, there is no conclusive evidence at present that the chemical composition of these bones is different from that of normal osseous tissue. One is forced to conclude that alterations in tensile strength are the result of morphologic rather than chemical differences.

CHEMICAL COMPOSITION OF MARBLE BONES

Five analyses of the chemical composition of the bones have been made. The results of these investigations are brought together in table 4.

TABLE 4.—*The Chemical Composition of Marble Bones*

	Calcium, per Cent	Phosphorus, per Cent	Magnesium, per Cent	Carbon Dioxide, per Cent	Water, per Cent
Normal children (Schabad: Arch. f. Kinderh. **52**: 47, 1910; cited by Hess, A. F.: Rickets, Including Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1929, p. 147)	21 to 28	12 to 20	0.10	...	13 to 32
Normal man, 50 years (Lauterburg)	28	22	1.67	4.2	16
Normal man, 26 years (Lauterburg)	30	22	0.44	...	24
Pirie [4]	29	..	....		
Kopyloff [33]	29	10	0.72		
Kudrjawtzewa [32]	29	20	....		
Péhu, Policard and Dufourt [18a]	"Normal"	"Normal"	?		
Lauterburg [17b]	33	26	0.36	3.9	15

In general, the chemical values relating to marble bones fall within rather wide normal limits. Although the analyses made by Kopyloff and Runowa [35] show a low phosphorus content and an elevated mag-

39. Parkinson, P.: M. J. Australia **2**:284, 1928.

nesium fraction, it is not possible to conclude from this single observation that osteopetrosis represents a fundamental alteration in the chemical composition of bone. One would expect the water content to be reduced, but the sole measurement of this constituent (Lauterburg [17b]) fell at the low limit of normal. The only analysis for carbonate content gave normal results.

The only deduction to be drawn from these investigations is a negative one, namely, that there is no evidence to indicate that osteopetrosis results from or produces a significant change in the quantitative chemical structure of bone.

As a matter of related interest, the analysis of the renal concretions which Péhu and his associates [18a] found in their patient revealed: ash, 83 per cent; phosphoric anhydride, 7.7 per cent; calcium (calcium oxide or calcium?), 22.4 per cent.

BLOOD CHEMISTRY IN OSTEOPETROSIS

The data concerning chemical alterations in the blood are scanty and are presented in table 5.

Schulze,[30] whose patient showed extensive calcification in the soft tissues, reported the blood calcium to be "double its normal value." Alter [29] stated that the blood calcium in his patient was "slightly high." Flood [40] noted persistent hypercalcemia (more than 15 mg. per hundred cubic centimeters) in his patient. Péhu, Policard and Dufourt [18a] did not give the values for their patient, but stated that the mother had a blood calcium level of 25 mg. per hundred cubic centimeters. Normal values on one or two examinations were reported by Pirie,[4] Clairmont and Schintz,[25] Bernhardt,[26] Kopyloff and Runowa [35] (slightly elevated on one determination), Kudrjawtzewa,[33] Sear,[41] Camauer and his associates,[42] Lauterburg, Cohn and Salinger,[43] Ghormley,[44] Ellinger,[45] Karshner [8] and Laurell and Wallgren.[13] The values for our patient were slightly low. Most of the authors failed to state the method

40. Flood, R. G.: Calcium Metabolism in Marble-Bone (Albers-Schönberg Disease), California & West. Med. **31**:203, 1929.

41. Sear, H. R.: A Case of Albers-Schönberg Disease, Brit. J. Surg. **14**:657, 1927.

42. Camauer, A.; Burlando, A., and Mortola, G.: Sobre un caso interesante de osteopatía marmórea de Albers-Schönberg (osteopetrosis), Rev. Soc. de med. int. y Soc. de tisiol. **7**:429, 1931.

43. Cohn, M., and Salinger, H.: Ueber ungewöhnliche Kalkanreicherung in den Gefässen und im Stützgewebe, Med. Klin. **23**:825, 1927.

44. Ghormley, R. K.: A Case of Congenital Osteosclerosis, Bull. Johns Hopkins Hosp. **33**:444, 1922.

45. Ellinger, E.: Ein Fall echter Marmorknochenerkrankung, Röntgenpraxis **1**:816, 1929.

TABLE 5.—*Chemical Alterations in the Blood*

Author	Serum Calcium, Mg. per 100 Cc.	Serum Phosphorus, Mg. per 100 Cc.	Whole Blood Sugar, Mg. per 100 Cc.	Whole Blood Chlorides, Mg. per 100 Cc.	Miscellaneous
Kudrjawtzewa [33]					
Female, 10 years.....	10	5.8	...	...	Potassium (serum), 20 mg. per hundred cubic centimeters; uric acid, 4.5 mg.
Llado [46]					
Female, 17 years.....	..	7.0			
Schulze [30]					
Male, 11 years.....	"Twice normal"				
Karshner [3]					
Male, 3½ years.....	"Normal"				
Female, 11 years.....	"Normal"				
Ellinger [45]					
Female, 18 years.....	10.2				
Ghormley [44]					
Male, 8 years.....	10.2	4.8			
Cohn and Salinger [43]					
Female, 18 years.....	10	...	93	...	Nonprotein nitrogen, 11 mg. per hundred cubic centimeters
Male, 48 years.....	11				
Davis [1]					
Male, 11 years.....	..	...	93	...	Nonprotein nitrogen, 34.3 mg. per hundred cubic centimeters
Camauer, Burlando and Mortola [42]					
Male, 19 years.....	9.8				
Sear [41]					
Male, 16 years.....	"Normal," 2 determinations				
Kopyloff and Runowa [35]					
Male, 20 years.....	11.6	...	...	...	Potassium (serum), 21, 26 and 21 mg.; sugar, sodium chloride and water tolerance tests gave normal results
	11.9	5.9			
	13.1	7.0			
	11.9	7.0			
	12.0	4.6			
	11.8				
Alter [29]					
Female, 8 years.....	"Rather high"	"Rather low"			
Bernhardt [26]					
Male, 25 years.....	10.3	...	116	585	Nonprotein nitrogen, 30.8 mg. per hundred cubic centimeters
After ammonium chloride.....	14.5				
Clairmont and Schintz [25]					
Female, 35 years.....	Whole blood, 6.8-11.4; normal, 5-10				
Pirie [4]					
Female, adult.....	"Normal," 2 determinations				
Flood [40]					
Female, 2 years.....	16.4				
	15.7				
	15.8				
	16.4				
	16.6				
	14.6				
Lauterburg [17b]					
Male, 33 years.....	12.5	...	...	...	Blood p_H 7.3
Laurell and Wallgren [13]					
Male, 12 years.....	....	...	150	...	Blood sugar after oral administration of dextrose: first hour, 260 mg.; second hour, 240 mg.; third hour, 160 mg.; fourth hour, 190 mg.
			150		
McCune and Bradley					
Female, 5 months....	9.4	3.8	117	524	Nonprotein nitrogen, 36, 27, 31 and 29 mg. per hundred cubic centimeters
	9.6	3.5	104	551	
	9.0	3.6	120	515	
	8.0	3.6	...	548	
	10.0	3.7			
	9.2	3.4			

employed in their determinations, and the normal values for the method. The same objection holds true for the phosphorus determinations. Alter stated that the level for his infant was "rather low." Llado [46] found a level of 7 mg. per hundred cubic centimeters for a 17 year old boy. Kopyloff and Runowa's figures are somewhat high for an adult, according to the present standards. The urinary excretion of calcium and phosphorus in single twenty-four hour periods was given by three authors.

	Calcium		Phosphorus	
	Mg.	Mg. per 100 Cc.	Mg.	Mg. per 100 Cc.
Kudrjawtzewa [33] (child)	247	12	684	36
Kopyloff and Runowa [35] (adult)	130	..	180	..
Clairmont and Schintz [25] (adult)	368	40		

The intake was not mentioned, and such figures are practically worthless.

A few isolated observations on the carbohydrate tolerance have been made (Laurell and Wallgren, Kopyloff and Runowa), but they provide no relevant data.

The basal metabolic rate was normal in three cases (Ellinger,[45] + 7.2; Ghormley,[44] + 11.1; Davis,[1] "normal").

METABOLIC STUDIES

Systematic observations on the calcium balance in Albers-Schönberg's disease were undertaken by Laurell and Wallgren,[13] Flood,[40] Bernhardt [26] and ourselves. We have included the determination of the phosphorus balance in our study.

Laurell and Wallgren performed a careful test of calcium metabolism on their patient, a boy of 12 years, who weighed 23.7 Kg. (52 pounds). Their study extended over twelve days, subdivided into six periods of two days each. The diet consisted of milk, cheese, butter and bread. It provided 69.3 Gm. of protein, 51.8 Gm. of fat and 168 Gm. of carbohydrate. The total energy value was 1,366 calories (57 calories per kilogram of body weight). The calcium intake averaged 1.830 Gm. of calcium oxide (1.31 Gm. of calcium) a day. Of this, an average of 1.403 Gm. of calcium oxide (1.012 Gm. of calcium) was excreted in the stools and 0.106 Gm. of calcium oxide (0.076 Gm. of calcium) in the urine, a total of 1.509 Gm. of calcium oxide (1.077 Gm. of calcium). The daily retention averaged 0.321 Gm. of calcium oxide (0.229 Gm. of calcium) or 0.013 Gm. of calcium oxide (0.0095 Gm. of calcium) per kilogram of body weight. The retention amounted to 17.3 per cent of the ingested calcium. Of that excreted 93.1 per cent appeared in the stools and 6.9 per cent in the urine. The authors commented on the

46. Llado, C.: Contribution à l'étude de la maladie marmoréenne des os, Rév. d'orthop. **18**:740, 1931.

difficulty in obtaining normal values. They cited a report of Alquist (reference not given), who obtained daily retention values of 0.058 and 0.044 Gm. of calcium oxide per kilogram in a normal child of about the same weight. Alquist's patient (a child) had a larger calcium intake. Laurell and Wallgren believed that, after making allowances for variable factors, it could be stated with certainty that their patient was not retaining an abnormally high quantity of calcium during the period of the investigation. From this they deduced that the disease was not in an active stage at the time of the study.

Flood [40] found that the serum calcium level was consistently elevated in his patient, a girl of 11 years, who weighed 21.6 Kg. (47½ pounds). The values on successive days were 16.4, 16.4, 15.7 and 16.6 mg. per hundred cubic centimeters. The diet at this time contained about 5.1 Gm. of calcium oxide (3.6 Gm. of calcium), a relatively high intake. During a three day period the child excreted 0.064 Gm. of calcium oxide (0.045 Gm. of calcium) in the urine (1.7 per cent) and 3.3 Gm. of calcium oxide (2.3 Gm. of calcium) in the stools (98.3 per cent). She retained a total of 0.560 Gm. of calcium oxide (0.4 Gm. of calcium) per day or about 0.028 Gm. of calcium oxide (0.02 Gm. of calcium) per kilogram per day. Although the blood values for calcium were high, the urinary excretion was low. It is well recognized that the hypercalcemia of hyperparathyroidism is usually associated with an increased excretion of calcium in the urine. When a second period of investigation was commenced one month later the blood calcium was found to have fallen to 14.6 mg. per hundred cubic centimeters. Flood was unable to produce either hypercalcemia or hypercalcuria with doses of 10 and 15 units of parathyroid extract. With 20 units the serum calcium level became elevated to 15 mg. per hundred cubic centimeters, although the urinary calcium was not increased. With 25 units there was an elevation of the serum calcium level and a slight augmentation in the urinary excretion. During a third period, following immediately on the experiments just mentioned, Flood was able to produce a small negative balance of 0.109 Gm. of calcium oxide daily by the administration of 25 units of parathyroid extract every thirty-six hours. In this period the serum calcium level reached 15.2, 15 and 15.3 mg. per hundred cubic centimeters. Vomiting caused the study to be terminated. Flood believed that his patient had an elevation of the renal threshold for calcium. Since the factors governing the excretion of calcium are so poorly understood, the concept of a "renal threshold" seems rather speculative.

The third metabolic study was that of Bernhardt. We have been unable to find the complete protocol of this experiment. Hence we have had to rely on a summary of his data published with the report of his case.[26] In this report Bernhardt stated only that the patient, a man,

26 years old, had a moderately positive calcium balance, and that the administration of relatively large doses of tertiary calcium phosphate did not result in more than normal retention of calcium. An attempt to produce a negative balance with "large doses" of ammonium chloride was "an almost complete failure." The serum calcium values were normal during the whole study except for an increase from 10.3 to 14.5 mg. per hundred cubic centimeters in association with the administration of ammonium chloride. The author stated that the patient felt better during this period, and that the blood picture showed some improvement.

Bernhardt was of the opinion that the bones in osteopetrosis have an increased affinity for calcium and that the liberation of the mineral is more difficult than under normal circumstances.

Calcium and Phosphorus Metabolism in the Authors' Patient.—Beginning ten days before the first period and continuing without change until the end of the last period, the child was given a formula made of whole powdered milk, distilled water and cane sugar. All feedings were prepared from the same can of powder, the calcium and phosphorus content of which had been determined by analysis. The beginning and end of each period was marked with carmine. The child was restrained on a suitable metabolism frame, and all excreta were collected for the duration of the periods. A special nurse was in charge of these collections. She recorded the refusal of food, vomiting or the loss of specimens. The calcium and phosphorus content of the refusals were subtracted from the total intake for that period. The vomiting and loss of specimens were negligible factors. The vomitus was not analyzed. A small correction was made for the estimated loss of urine. There was no loss of stools.

The experiment was divided into three periods. Each period was preceded and followed by an interval of ten days to allow the infant to reach equilibrium. During the first period the child received the formula alone, without added medication. In the second period 8 cc. of cod liver oil was given daily. This was discontinued at the end of the period. In the course of the third period 10 units of parathyroid extract was injected intramuscularly on each of three successive days. The child was kept in the open ward, but was not exposed to direct sunlight. The windows were of ordinary plate glass, not significantly permeable to ultraviolet rays. The weather was warm and the windows were kept open a large part of the time.

The chemical determinations were done on aliquots of the total amount of urine and the pooled feces of an entire period. Calcium determinations were done by the method of McCrudden [47] on 200 cc.

47. Peters, J., and van Slyke, D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 761.

of urine and 7.5 Gm. of dried and powdered stool after dry ashing at temperatures not exceeding 500 C. Phosphorus was determined by the gravimetric method of Mackay and Butler,[48] using 50 cc. of urine and 3 Gm. of dried and powdered stool after preliminary wet ashing with sulphuric and nitric acids aided by superoxol. The magnesium ammonium phosphate was converted to magnesium pyrophosphate before weighing.

The diet, consisting of 60 Gm. of whole powdered milk, 30 Gm. of cane sugar and distilled water to 600 cc., provided a total of 420 calories a day, or 105 calories per kilogram of body weight per day, and a fluid intake of 600 cc. a day, or 150 cc. per kilogram of body weight per day. The patient, 5 months of age and 55 cm. in length, had an approximate weight of 4,100 Gm., or a calculated weight for length of 5,000 Gm.

The chemical data appear in table 6.

Comment.—1. The balance of both calcium and phosphorus was strongly positive during all three periods. The quantity retained per kilogram of body weight was calculated on the basis of both the actual weight and the ideal weight of a normal infant of the same length.

It is impossible to determine from these figures what effect the osteopetrosis alone had on the retention of calcium and phosphorus. There are several reasons for this difficulty: First, the infant had severe rickets; roentgen examination indicated that the rickets was in the stage of healing. Second, the infant had an almost constant infection of the upper respiratory tract. Third, we are unable to find in the literature a sufficient number of standard values, obtained with the same sort of diet, to enable us to determine what the child's "normal" retention should have been. The numerous complexities resolve themselves into the task of finding "normal" values for an infant of the same age, presenting the same degree of undernutrition with an identical grade of rickets, having a persistent infection of the upper respiratory tract and receiving the same diet. Obviously such a quest was hopeless. The problem could hardly have been solved by performing a parallel metabolic study with a normal infant as a control.

In general terms, the retention which our patient showed was high. Swanson [49] fed a single nonrachitic, healthy infant a diet comparable with ours, and noted that the infant retained 0.023 Gm. of calcium per kilogram daily and 0.019 Gm. of phosphorus. When cod liver oil was added, the retention was increased to 0.045 Gm. of calcium per kilogram and 0.022 Gm. of phosphorus.

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48. Peters and van Slyke,[47] p. 858.

49. Swanson, W.: The Composition of Growth: II. The Full-Term Infant, Am. J. Dis. Child. **43**:10 (Jan.) 1932.

Daniels, Stearns and Hutton [50] fed a large group of infants mixtures of boiled and pasteurized milk with added dextrimaltose or lactose. The calcium intake was 0.89 Gm. daily, and the phosphorus intake 0.71 Gm. The infants were said to be nonrachitic. With feedings of

TABLE 6.—*Results of Metabolic Study of Calcium and Phosphorus Retention*

	Calcium			Phosphorus		
	Per Period	Per Day	Mode of Excretion	Per Period	Per Day	Mode of Excretion
Period I. 12 Days (Sept. 9 to 20); Average Weight, 4,186 Gm.; No Medication						
Output						
Urine	0.2299	0.0191	10%	2.7300	0.2270	84%
Stool	2.0880	0.1740	90%	0.5140	0.0427	16%
Total	2.3179	0.1931	100%	3.2440	0.2697	100%
Intake	6.8152	0.5677		5.2510	0.4208	
Balance	4.5973+	0.3746+		2.0070+	0.1511+	
Retention, mg./Kg./day						
Actual weight	89.5 mg.			36.2 mg.		
Ideal weight	75.0 mg.			30.0 mg.		
Percentage of intake retained	66			38		
Ratio: Calcium retained to phosphorus retained: 2.48						
Period II. 10 Days (Oct. 2 to 11); Average Weight, 4,117 Gm.; Cod Liver Oil, 8 Cc. Daily						
Output						
Urine	0.2330	0.0230	14%	1.9230	0.1923	84%
Stool	1.4250	0.1425	86%	0.3057	0.0305	16%
Total	1.6550	0.1655	100%	2.2287	0.2287	100%
Intake	5.7360	0.5736		4.4215	0.4421	
Balance	4.0810+	0.4081+		2.1928+	0.2192+	
Retention, mg./Kg./day						
Actual weight	99.2 mg.			53.2 mg.		
Ideal weight	81.6 mg.			43.0 mg.		
Percentage of intake retained	71			45		
Ratio: Calcium retained to phosphorus retained: 1.86						
Period III. 5 Days (Oct. 24 to 29); Average Weight, 4,155 Gm.; Parathyroid Extract, 10 Units Daily on Three Days						
Output						
Urine	0.0884	0.0176	16%	1.0810	0.2039	88%
Stool	0.4783	0.0956	84%	0.1399	0.0279	12%
Total	0.5667	0.1132	100%	1.1579	0.2317	100%
Intake	2.8800	0.5760		2.2200	0.4440	
Balance	2.3133+	0.4628+		1.0621+	0.2223+	
Retention, mg./Kg./day						
Actual weight	110.5 mg.			53.7 mg.		
Ideal weight	92.0 mg.			44.0 mg.		
Percentage of intake retained	83			48		
Ratio: Calcium retained to phosphorus retained: 2.08						

pasteurized milk the infants retained about 0.004 Gm. of calcium and 0.007 Gm. of phosphorus per kilogram daily. When the feedings were made of boiled milk the retentions increased to 0.014 Gm. of calcium

50. Daniels, A.; Stearns, G., and Hutton, M.: Calcium and Phosphorus Metabolism in Artificially Fed Infants: I. Influence of Cod Liver Oil and Irradiated Milk, Am. J .Dis. Child. **37**:296 (Feb.) 1929.

and 0.011 Gm. of phosphorus. In a group of infants who had had cod liver oil before the experiments the retentions of both minerals were about 0.025 Gm. per kilogram per day. In a third group of infants who had cod liver oil both before the experiment and during it, the retention values approximated 0.03 Gm. per kilogram.

Nelson [51] fed a large group of well nourished, nonrachitic infants a mixture of whole lactic acid milk with added corn syrup and 4 cc. of cod liver oil daily. There were nine infants of the same age as our patient (6 months). The intake of calcium was 1.162 Gm. and of phosphorus, 0.924 Gm. With these quantities, which are considerably larger than ours, Nelson found that the infants retained 0.064 Gm. of calcium per kilogram per day and 0.033 Gm. of phosphorus. Although the retention which our patient showed exceeds any of these figures, the increase over Nelson's results is not striking, and there is nothing which enables us to evaluate the relative influences of the osteopetrosis and the healing rickets.

2. Our patient retained a high percentage of the total intake of both minerals. Although one can increase the actual retention of calcium and phosphorus by increasing the amounts fed, the ratio of retention to intake decreases as the amount ingested increases. Conversely, on a diet low in these elements the percentage retained may be high. On diets of diluted milk containing from 0.56 to 1.18 Gm. of calcium, Holt [52] observed that from 30 to 39 per cent was retained. Daniels [50] found this value to be around 30 per cent. Nelson's [51] figure is 41 per cent. For phosphorus, Daniels gave a value of 25 per cent and Nelson 30 per cent. These investigators were using diets the calcium and phosphorus content of which was considerably higher than ours. Holt also made the observation that the retention is higher in undernourished infants (39 per cent) than in well nourished infants (30 per cent). It is not necessary to add that there is an increased retention of both elements during the period of recovery from rickets.

From these statements it is obvious that the increased utilization of calcium and phosphorus which our patient showed cannot be related directly to osteopetrosis.

3. It will be observed that, of the calcium excreted, between 10 and 16 per cent appeared in the urine and the remainder in the stools. Low urinary calcium is characteristic of the bottle-fed infant. The slight but definite increase following the administration of cod liver oil is a

51. Nelson, M.: Calcium and Phosphorus Metabolism in Infants Receiving Undiluted milk, Am. J. Dis. Child. **42**:1090 (Nov.) 1931.

52. Holt, L. E.; Courtney, A., and Fales, H.: Calcium Metabolism of Infants and Young Children and the Relation of Calcium to Fat Excretion in the Stools: I. Infants Taking Modified Cow's Milk, Am. J. Dis. Child. **19**:97 (Feb.) 1920.

common phenomenon and is regarded as signifying an increased absorption of calcium from the alimentary tract.

The relationship between the urinary and the fecal phosphorus was normal. There is an increase in the quantity of phosphorus excreted by way of the intestines during active rickets. In severe cases the quantity so excreted may reach or even exceed that passed in the urine. The fact that the relationship between the two modes of excretion was normal may be regarded as added evidence that the rachitic process was not active at the time of the study.

These normal relationships constitute strong evidence against the existence of hyperparathyroidism. In the latter condition there is an increase in the urinary calcium and augmentation in the percentage of phosphorus excreted in the stools.

4. The ratio of the calcium retained to the phosphorus retained has been a subject of interest to many investigators. Our patient showed values of 2.48, 1.86 and 2.08.

Daniels and his associates [50] obtained retention ratios of 0.5 on a diet of pasteurized milk without cod liver oil, 1.2 with boiled milk without cod liver oil, 1.2 and 1.4 with boiled milk and cod liver oil and 2 when the infants were fed irradiated milk. Nelson's [51] ratios varied from 1.3 to 2.3, with an average of 1.75. Swanson's [49] infant had a ratio of 1.2 without cod liver oil and 2 when cod liver oil was added.

In general, antirachitic substances tend to increase the retention of both calcium and phosphorus in such a manner that their retention ratio approaches the values found in the blood serum and in bone. In the blood serum the relationship is approximately 2:1. If bone is composed largely of tricalcium phosphate ($Ca_3[PO_4]_2$), the ratio for bone is 1.94. If Hastings' formula [53] for the mineral matter of bone is correct ($CaCO_3 \cdot 2\,Ca_3[PO_4]_2$), the ratio is 2.26. During the period of growth, calcium is retained largely for the purpose of the formation of bone, whereas phosphorus serves many other purposes. For this reason the retention ratio is always lower than it would be if the total conservation of these electrolytes was due to the formation of bone. Under circumstances in which the production of bone dominates the metabolic situation, the ratio tends more closely to approximate the higher values.

Our patient showed no increase in weight or length during the period of observation. However, there was roentgenographic evidence of rapid ossification in the rachitic areas of the skeleton. It seems reasonable to assume that a large proportion of the retained minerals was employed

53. Roseberry, H.; Hastings, A. B., and Morse, J.: X-Ray Analysis of Bone and Teeth, J. Biol. Chem. **90**:395, 1931. Bogert, J., and Hastings, A. B.: The Calcium Salts of Bone, ibid. **94**:473, 1931.

in the formation of this bone. This surmise affords a tentative explanation of the consistently high ratio.

5. We can offer no satisfactory reason for the failure of the characteristic effect of parathyroid extract. There was no indication to question the potency of the preparation. Unfortunately, the blood calcium and phosphorus were not determined during the period of administration of parathyroid extract. Twelve days had elapsed since the end of the period during which cod liver oil was given. Possibly this interval should have been longer. A dosage of 10 units would seem adequate to produce an increase in the urinary calcium in so small an infant. The period was shortened to five days, so that the expected effect of parathyroid extract would be more obvious.

We can only add this observation to those of Flood [40] and Bernhardt,[26] who also had difficulty in producing a negative balance in their patients, the former by the use of parathyroid extract and the latter with ammoium chloride. There is nothing in the clinical history of any of the cases to suggest hypoparathyroidism.

The fact that calcium and phosphorus were actually retained in greater quantities during the period in question suggests that some potent antirachitic factor was at work. We cannot say whether this lay in the persistent effect of the dosage of cod liver oil, discontinued twelve days earlier, or whether the light of the ward was the active agent. It may be mentioned that Hoag and Rivkin [54] made a similar observation of increased retention in an infant with tetany whom they were treating with parathyroid extract.

In summary, our results showed a rather high retention of calcium and phosphorus, with a normal partition of the excreted elements between the urine and stools. The percentage of retention of the ingested electrolytes was also high, as was the ratio of the retained calcium to the retained phosphorus. The administration of cod liver oil served to increase the retention of both calcium and phosphorus. The retention of phosphorus was augmented more than that of calcium, and the calcium-phosphorus ratio fell slightly. The administration of 10 units a day of parathyroid extract failed to produce a negative balance, but was accompanied by a further increase in the retention of both elements.

CLINICAL ASPECTS

Most cases of Albers-Schönberg's disease have been diagnosed on the basis of roentgen examination made because of the occurrence of pathologic fractures or in the hope of obtaining aid in the explanation

54. Hoag, L.; Rivkin, H.; Weigele, C., and Berliner, F.: Effect of Potent Parathyroid Extract on Calcium Balance in Infants, Am. J. Dis. Child. **33**:910 (June) 1927.

of a puzzling clinical problem. While it is not possible to assert that the less typical examples occurring in adults should be recognizable without roentgenographic aid, the clinical picture in infants and young children is usually characteristic. If the proper points are kept in mind the diagnosis may be made with a high degree of probability before resorting to the use of roentgen rays. In the interests of a systematic presentation, although possibly at the expense of weakening the proof of this contention, the roentgenographic features will occupy a prominent place in the following discussion.

Changes in the Osseous System.—These consist essentially in: (I) increased roentgenographic density of the entire skeleton and (II) marked increase in the fragility of the bones, which manifests itself in the frequent occurrence of pathologic fractures. The former constitutes a diagnostic *sine qua non*; the latter is an important anamnestic point which suggests the presence of osteopetrosis.

I. The roentgenographic aspects of the disease are summarized in the following description which is taken with some modification from Lauterburg:[17b] A. There is marked increase in the density of the roentgen shadow of the skeleton, with complete or partial loss of the normal structure of the bones. The shadow of the marrow cavity is reduced, sometimes to the point of complete obliteration. These changes are usually generalized, although frequently the humeri, the bones of the lower arm and those of the lower jaw are less involved than the rest of the skeleton. In a few cases there have been areas of actual osteoporosis (Kudrjawtzewa and Schulze). The most striking increase in density occurs in the vertebral bodies, the central part of the pelvis, the base of the skull, the upper third of the femurs and the lower third of the tibias and fibulas.

B. There are peculiar alterations in the roentgenographic structure of bone both in adults and in children, although they are less common in the latter. These consist in: (1) "stratification," or the appearance of transverse bands of alternating greater and less density parallel to the epiphyseal line on the shafts of the long bones. The bands vary in width and number. They may be limited to the ends of the shafts or they may be present through the whole diaphysis. Such changes are seen most commonly in the distal ends of the femurs, in the proximal ends of the tibias, in the metacarpal and metatarsal bones and in the phalanges.

The flat bones of the pelvis and the small bones of the tarsi and carpi may show bandlike shadows of varying density arranged parallel to the outline of the bone. This phenomenon may produce the impression of a circular defect in the bone. Sear's[41] first patient showed radial striations in the pelvic bones alined in a fanlike manner.

(2) There may be enclosures of sharply demarcated foci of compact bone, the outline of which is similar to that of the bones in which they are included. These are seen in the metacarpal and metatarsal bones, the phalanges and the ribs.

C. Clublike thickening of the posterior clinoid processes and narrowing of the sella turcica are invariable findings. One should hesitate to confirm the diagnosis of osteopetrosis in the absence of these features. Frequently, but not invariably, there is symmetrical widening of the ends of the long bones. This is usually designated as clubbing (*dilatation en massue; keulenförmige Verdickung*). It is most common at the proximal ends of the humeri and the distal ends of the femurs.

D. Aside from the clubbing, other changes in the contour of the bones are uncommon. Shadows suggesting periosteal disturbances were noted by Windholz [37] (one case), Priesel [38] (two cases) and Frank [31] (one case). Marque's [55] two patients also had thickening of the periosteum, but the Wassermann reaction of the blood was positive in both cases.

E. Fractures are frequently present. It is interesting that roentgenograms frequently disclose evidence of old fractures of the occurrence of which the patient was not aware. There is usually evidence of normal healing of these fractures with the production of abundant callus. However, delayed union has been described in several cases. Instances are reported in which the line of fracture was demonstrable roentgenographically many years after the complete restitution of function. Deformity of varying degree may be present as the result of the fractures.

F. With few exceptions there is no interference with the time of the appearance of the centers of ossification or the fusion of the epiphyses with the shafts. The centers of ossification share in the sclerosing process.

G. Roentgenographic evidence of concomitant suppurative disease of the bones is fairly common. The parts usually involved are the maxilla, mandible, femurs and scapulas.

H. The presence of rickets has been noted by three observers (Karshner,[8] Kudrjawtzewa,[33] McCune and Bradley).

II. Increased fragility of the bones is, in many cases, recognized during infancy and childhood, and in practically all persons whose condition has been diagnosed in adult life the presence of one or more fractures has been noted. Frequently the physician is consulted solely because of this symptom. This is true of Albers-Schönberg's original

55. Marque, A.: Dos casos de osteoesclerosis en el niño, Semana méd. **34**:581, 1927.

patient. One of Sick's [56] children had fourteen fractures. Such fractures occur as the result of relatively trivial causes. It is generally stated that they are not attended by pain, may be unrecognized by the patient and may be brought to light only by subsequent roentgen examination. This is not always true, for severe pain is sometimes present. It is probable that the presence or absence of pain is dependent on periosteal involvement. Many of the fractures are sharply transverse, without splintering or displacement of the fragments and without evidence of injury to the periosteum. Displacement of the fragments is evident in the cases in which pain is specifically mentioned. As has been stated, the fractures usually heal promptly. However, in Alexander's [2] patient healing was delayed for over two years. Bernhardt's [26] patient showed "poor healing," and one of Lauterburg's [17a] patients had chronic osteomyelitis about the site of fracture which prevented healing for so long that amputation was performed.

The Blood Picture.—The presence of anemia, while not invariable, is common. The anemia is usually of the hypochromic variety, with a color index of less than 1, although instances of the hyperchromic type have been recorded. The degree of anemia is variable. There is a definite lack of parallelism between the severity of the anemia and the roentgenographic appearance of the bones. There are several cases on record in which the roentgen shadow of the skeleton suggested complete obliteration of the marrow cavity, but in which the blood picture was essentially normal. The reduction in the number of red cells and in the quantity of hemoglobin may be marked before death. This was illustrated in Albers-Schönberg's [12b] patient and in our own. Anemia is frequently associated with the presence of varying numbers of immature red cells, usually normoblasts. Megaloblasts may be present. In adults with anemia the number of white blood cells is generally normal or slightly reduced. Infants are more prone to show leukocytosis, which is characterized by the presence of moderate numbers of immature myeloid cells.

Reports of the estimation of the blood platelets are not numerous. Reiche [12b] stated that the number of blood platelets in Albers-Schönberg's patient was normal up to the time of death. Kopyloff and Runowa [35] gave values varying between 350,000 and 180,000 per cubic millimeter. In Nadolny's patient the platelets numbered only 50,000. Frank [31] stated that the number of platelets was "normal" in one of his patients, 60,000 in a second and 70,000 in a third. Our own patient showed marked thrombocytopenia (as low as 20,000 per cubic millimeter), which was

56. Sick: Ueber drei Fälle einer seltenen Skeletterkrankung, in Festschrift zur Feier des 25 jährigen Bestehens des Eppendorfer Krankenhauses, Leipzig, Leopold Voss, 1914. (Forms vol. 36 of: Jahrb. f. Psychiat. u. Neurol.)

ultimately associated with purpura. The literature contains little concerning hemorrhagic manifestations. Alter's [29] patient had subperiosteal hemorrhages.

Measurements of the bleeding and clotting time, the blood sedimentation rate and the resistance of the red cells to hypotonic saline solution have been made so infrequently that little is known of these features. Laurell and Wallgren [18] found sharp lymphocytosis following the subcutaneous administration of epinephrine. This was followed by an increase in the number of polymorphonuclear cells.

Many authors explain the blood changes by the simple assumption that the increased quantity of bone crowds the marrow out of existence in a more or less mechanical way. This hypothesis would imply a certain amount of parallelism between the degree of sclerosis and the severity of the anemia. Such correlation is not always present. It is not difficult to explain the absence of marked changes in the blood in certain cases in which the bones appear to be exceedingly dense and in which the marrow cavity is apparently completely occluded. In such cases one may assume that the cortex is so thick that it prevents the passage of the roentgen rays and produces, thereby, the false impression of obliteration of the medullary canal. There are, however, a few cases in which the anemia seemed more severe than the amount of roentgenographic changes in the bones would lead one to expect. This type of case suggests that the marrow itself may be at fault. We shall discuss this point in the section on the etiology of the disease.

Hyperplasia of the Lymphoid Tissue.—The published data suggest that there is a regular parallelism between the presence and degree of anemia and the enlargement of the superficial lymph nodes, the spleen and the liver. Both findings are more common in infantile cases. Laurell and Wallgren,[18] Lorey and Reye [32] and Schulze [30] held the view that this hyperplasia was an expression of compensatory hematopoiesis in the extramedullary blood-forming organs. The contradictory pathologic observations concerning this point have already been summarized. Two or three authors have reported hemosiderosis in the tissues under discussion. The rôle of the extramedullary blood-forming apparatus in osteopetrosis is still uncertain.

Hydrocephalus.—Increase in the size of the head or frank hydrocephalus was mentioned by Scharsich,[57] Sick,[56] Sear,[41] Alter,[29] Lorey and Reye [32] (two cases), Karshner,[3] Kudrjawtzewa [33] (three cases), Kraus and Walter [27] and others. It was present in our patient. One or two authors have mentioned mild exophthalmos without specific mention of the appearance of the head or its measurements. Hydrocephalus seems to be more common in young patients, and is almost the rule in those

57. Scharsich, K.: Ueber Marmorknochen, Beitr. d. klin. Chir. **151**:561, 1931.

whose conditions are diagnosed in early infancy. It is not referred to in adult patients, a fact which makes one suspect that persons so stigmatized do not survive. Hydrocephalus is apparently a manifestation of a severe form of the disease. Several reports contain the statement that there were other infants in the same family who had large heads and who died within the first year or two of life.

There are few data on which to base an opinion as to the type of the hydrocephalus. Lorey and Reye reported the pressure of the spinal fluid as varying between 400 and 620 mm. of water in one of their patients (2½ years of age). It was 600 mm. in another (2 years of age) and 450 mm. in a third. All had clinical hydrocephalus. The pressure was reported as "high" in one of Karshner's patients with hydrocephalus and also in Nadolny's case. Laurell and Wallgren [13] found a pressure of 330 mm., which fell to 220 mm. after the withdrawal of 10 cc. of fluid. Our patient showed a pressure of 530 mm. of water. Kopyloff and Runowa [35] observed that their adult patient without evidence of hydrocephalus had a spinal fluid pressure of 220 mm. All values except the last one are definitely elevated. We have been unable to find any data based on the use of intraventricular injections of dye. No subdural taps (punctures of the fontanel) have been performed, and apparently there have been no studies made using spinal encephalography or ventriculography.

Narrowing of the foramina of the skull has been found at autopsy in a few cases (Lorey and Rye,[32] Kraus and Walter,[27] Alter [29]), although one or two attempts to demonstrate this by roentgenography during life have been unsuccessful. Most authors assume that the hydrocephalus is due to constriction of the cranial ostia. The mechanics of this process is not described. Since the circulation of the cerebrospinal fluid takes place largely within the skull, it is difficult to understand why occlusion of the foramina should have any direct effect in the production of hydrocephalus. Since, however, the degree of intracranial pressure varies directly with alterations in the venous pressure within the skull, it is possible that obstruction to the venous outflow might lead indirectly to hydrocephalus. Add to this the possibility of hemorrhage due to vascular distention, with the production of pachymeningitis interna haemorrhagica (chronic subdural hematoma), and it becomes probable that narrowing of the foramina may be a factor of importance. In this connection it is important to note that Lorey and Reye [32] demonstrated hydrocephalus and pachymeningitis interna haemorrhagica at autopsy in one of their cases. Kraus and Walter showed anatomically that their patient had internal and external hydrocephalus combined with thickening of both the dura mater and the leptomeninges. Our case showed considerable dilatation of the superficial veins of the scalp, a

physical sign frequently associated with chronic subdural hematoma. It is greatly to be regretted that this possibility was not investigated during life.

We are unable to comment on the significance of the observation of Camauer and his associates,[42] who stated that their patient showed acrocephalia and hypertelorism. It is the only observation of the kind which has been reported in association with osteopetrosis.

Neurologic Complications.—Optic atrophy is an almost invariable concomitant of hydrocephalus and has been recorded in a few cases without obvious enlargement of the head. Laurell and Wallgren [13] are apparently the only authors who observed papilledema. Corresponding to the degree of atrophy, the visual disturbances vary from moderate loss of acuity to complete blindness. Nystagmus is occasionally present, and apparently is always associated with the impairment of sight. An explanation of the optic atrophy is suggested by the postmortem observations of Schulze,[30] Lorey and Reye [32] and Alter.[29] They found the optic foramina distinctly narrowed as the result of thickening of the bones, and assumed that the atrophy was due to compression of the optic nerve. Optic atrophy is a common sign of pachymeningitis. If the speculations in which we have indulged are valid, it is possible that the changes in the eyegrounds in some cases of osteopetrosis may have an alternative explanation. We have been unable to discover any mention of retinal hemorrhages.

Alexander [2] reported a slight degree of facial paralysis associated with difficulty in speech. Kopyloff and Runowa's [35] patient showed some facial weakness and that of Clairmont and Schintz [25] presented a labyrinthine type of deafness with extra-ocular palsy. These symptoms are also ascribed to the compression of nerve trunks as they pass through the cranial foramina. The inconstancy of such features gives rise to legitimate doubt concerning their fundamental relationship to the Albers-Schönberg syndrome.

Osteomyelitis.—Dental caries has been observed in nearly all patients of sufficient age to have erupted teeth. In a number of instances there has been osteomyelitis of the maxilla or mandible (Reiche,[12b] Sick [56] Lorey and Reye,[32] Laurell and Wallgren,[13] Bernhardt,[26] Edel [34] and Sear [41]). In many of these patients this complication was followed in a short time by death. In other cases the infection was indolent.

Kopyloff and Runowa [35] and Davis [1] reported separate instances of osteomyelitis of the scapula and Kudrjawtzewa [33] and Bernhardt [26] mentioned the presence of chronic infection in the fingers. The patients of Lauterburg and of Parkinson had chronic suppurative processes about the site of old fractures.

Developmental Features.—The disease is characterized by retardation in growth in length and delay in the development of secondary sexual

characteristics. Dentition is said to occur late, although this is not a uniform feature. In one of Kudrjawtzewa's [33] patients and in our own the appearance of the unerupted teeth was normal by roentgenogram. In addition to constitutional factors tending to retard growth, many of the patients have shortened stature as the result of the numerous fractures. The characterization *gracile habitus* appears in several reports, and it is stated frequently that the patient looked several years younger than the chronological age.

In contrast to the retarded physical development, the patients who survive infancy appear to be of good mentality. No significant psychic disturbances have been reported. There are no detailed data concerning the mental status of the hydrocephalic children, but the majority are described as mentally alert. The presence of blindness makes the precise estimation of the mentality of a hydrocephalic infant a matter of considerable uncertainty.

Constitutional Symptoms.—Subjective disturbances seem to be conditioned primarily by the presence of anemia and its severity. Repeated fractures may produce a varying amount of incapacity which depends on the rapidity with which healing is accomplished and on the residual deformity. Vague pains in the back and extremities have been present in a few instances. Whether they are symptomatic of unrecognized fractures or whether they represent painful proprioceptive sensations resulting from structural changes in the bones is entirely speculative. That the symptom of pain is usually lacking is probably due to the fact that the periosteum is not involved in a manner which produces sudden stretching.

As a corollary to what has been said, there is no parallelism between the degree of roentgenographic alteration in the bones and the severity of the constitutional symptoms. The patient of Albers-Schönberg was active for eleven years after the first observation. At that time he was the head of a commercial firm, and his only complaints were that he had an enormous appetite and required a good deal of rest. Bonta's [58] patient led an active life as a farmer and Parkinson's [39] patient saw service in the World War.

Parental Consanguinity.—Consanguinity on the part of the parents was reported by Lorey and Reye,[32] Alexander,[2] d'Istria,[59] Cohn and Salinger,[43] Kudrjawtzewa,[33] Llado,[46] and Windholz.[37] It was present in our case. Sick's [56] family came from Helgoland Island, where inbreeding has been current for generations. Usually the relationship is stated to be that of "cousin." The presence of consanguinity was

58. Bonta, M. B.: A Case of "Marble-Bone" Disease, Proc. Staff Meet., Mayo Clin. **3**:10, 1928.

59. d'Istria, A.: Su di un caso di "Marmorknochen" malattia di Albers-Schönberg, Radiol. med. **15**:473, 1928.

specifically denied by Kopyloff and Runowa,[35] Lauterburg,[17b] Ellinger,[45] Bernhardt [26] and Edel.[34] In the remaining reports this factor was not mentioned.

Kudrjawtzewa stated that both parents had been married before. The father had had three normal children by the first marriage and the mother one normal child. By their consanguineous marriage they had five children, two of whom died in infancy and three of whom had typical osteopetrosis. D'Istria noted the same coincidence. The father had three normal children by a previous marriage. Union with a cousin resulted in five children; three died in infancy. Of the remainder, one was mentally defective and the other had marble bones.

Familial Features of the Syndrome.—Albers-Schönberg's disease shows a strong familial tendency. The three cases reported by Lorey and Reye [32] occurred in sisters; Sick's [56] patient was a cousin in the same family. Pirie [4] reported the disease in a mother and her three offspring. Kudrjawtzewa,[33] Cohn and Salinger,[43] and Frank [31] each found osteopetrosis in three children in the same family. Lauterburg's [17a] two patients were brothers. Llado [46] was unable to study the other members of the family of his patient, but stated that the child had two brothers, both of whom died in infancy. One had been known to have a large spleen, and the other was blind from birth. Many reports fail to mention the number and physical status of the other children. The history of one or more miscarriages is given several times. In several families, also, there is mention of a number of children who died in infancy. We have cited d'Istria's [59] experience. The 1 year old brother of Edel's [34] patient suffered from some organic nervous disease accompanied by convulsions. Of the seven children in the family of Alexander's [2] patient, four died of "children's diseases" before the age of 5 years.

We were unable to discover evidence of the disease in the living members of the family of our patient. However, two infants in this family died at the age of 4 months, one of "bronchitis" and the other following an operation for the removal of adenoids. The need for such an operation at this age suggests the possibility of a condition comparable to that of our patient.

Heredity.—With three exceptions the victims of this disease seem to have been childless. As already mentioned, Pirie's [4] oldest patient was the mother of three children, all of whom had marble bones. Pirie had the good fortune to make a roentgen examination of the mother during pregnancy and, because of the density of the fetal skeleton, hazarded the guess that the offspring, too, had osteopetrosis. This diagnosis was confirmed by later observations on the child. Ghormley [44] reported the disease in a father and son. Alexander's patient was a woman who had five children, all of whom were in good health. Appa-

rently they were not studied closely for evidence of osteopetrosis. It may be concluded that the disease may be transmitted from parent to child. This, however, happens infrequently.

Age Incidence.—As has been stated, Albers-Schönberg's disease has its onset predominantly in infancy and childhood. This is demonstrated in table 7, in which the cases are grouped according to the age of the patient when the diagnosis was made. It must be emphasized that many of the patients who do not come under medical observation until adult life give a history of pathologic fractures extending back to early childhood. Regardless of the age at which the patient presents himself, it is usual to find the disease fully established at that time.

TABLE 7.—*Ages of Patients at Time of Diagnosis*

		Number of Cases
Childhood		37
1 to 6 months	9	
6 to 12 months	7	
1 to 6 years	8	
6 to 12 years	13	
Adults		27
12 to 20 years	9	
20 to 30 years	8	
30 to 40 years	6	
40 to 50 years	2	
50 to 60 years	1	
60 to 70 years	1	
Age not known		2

TABLE 8.—*Countries from Which Reports of Cases Have Come*

Germany	18	Switzerland	4	Scandinavia	2
United States	14	Holland	3	France	1
Canada	5	Australia	3	Japan	1
Russia	4	Austria	2	Italy	2
South America	4	British Isles	2	Spain	1

Certain cases demonstrate clearly that the disease may begin in early intra-uterine life and be fully developed at the time of birth. Many authors state that the onset may be delayed until adult life. Although this possibility cannot be denied, there is no case on record in which this onset has been observed and followed roentgenographically after the period of childhood. Pirie's [4] series is the only one to our knowledge in which the first stages of the disease have been seen. Pirie's patients were children.

Sex.—Of the sixty-six cases which comprise our list thirty-four were in females and twenty-seven in males; the sex of the remaining five was not given.

Racial Features.—The ethnic stock of the patients is rarely mentioned. We have thought it interesting to prepare a table showing the countries from which the reports of the cases emanated.

ETIOLOGY

The etiology of Albers-Schönberg's disease is unknown. Some commentators have suggested that the cases grouped under this heading do not represent a disease sui generis, but show simply a symptom complex resulting from the operation of various causes and lack a common etiologic factor. This possibility has not been strongly emphasized, and most writers regard the disease as a true pathologic entity. All agree, however, that its relationship to certain other combined diseases of the bones and blood-forming organs may be close. It has been pointed out earlier in this paper that the selection of cases is difficult. Either through lack of data or because of the equivocal nature of the findings, certain cases are exceedingly hard to classify in one group or another.

Osteopetrosis is a rare disease. For this reason the number of cases in the experience of a given author has not been large. A few have been fortunate enough to observe two or three examples in the same family. Even in such instances the amount of pathologic and chemical data collected has been small. Despite this paucity of individual experience, or possibly because of it, there has been an excessive tendency toward broad generalization of the basis of features peculiar to a single case.

The father of Albers-Schönberg's [11b] patient was syphilitic. This fact led Reiche [12b] to regard the disease as a manifestation of syphilis. There are, however, only two other cases in the literature (Marque [55]) in which there was serologic evidence of syphilis. We believe that this infection can be excluded categorically as a factor of etiologic importance.

Lorey and Reye [32] attributed osteopetrosis to polyglandular dyscrasia. They treated three patients with pituitary extract by mouth, but observed no improvement. On the basis of delayed epiphyseal union and a small thyroid gland Laurell and Wallgren [13] also sought to incriminate the ductless glands, notably the thyroid and pituitary. M. B. Schmidt [22] found a small hypophysis at autopsy, and thought that this represented a causal factor. Narrowing of the sella turcica is a characteristic feature of the disease, but most writers regard this change as secondary and not indicative of a primary disturbance in the hypophysis. In none of the cases reported have diabetes insipidus, acromegaly or excessive adiposity been found. The few determinations of the basal metabolic rate have given normal values.

Péhu and his associates [18a] found a parathyroid adenoma in their patient. This was associated with large masses of calcium in the renal pelves. The authors suggested that the syndrome is the result of hyperparathyroidism, and expressed the belief that it is closely related to osteitis fibrosa cystica. Pathologic deposits of calcium were also present

in Schulze's [30] case. Here, and in several other cases, the parathyroid glands were normal. Schulze [60] assumed, however, that the disease is due primarily to disturbance in the calcium metabolism. The essential feature of this disturbance is a hypothetic interference with the renal excretion of calcium. Nadolny,[28] apparently by a process of exclusion, also located the seat of the trouble in the calcium metabolism. Llado [46] arrived at the same conclusion without convincing proof. Kopyloff and Runowa [35] expressed the belief that the mechanism of the disturbance is primarily a chemical one in which there is a diminished excretion of calcium, and as the result, an excessive amount of calcium is brought to the tissues and deposited there. They assumed that the dyscrasia results from avitaminosis. Kudrjawtzewa [33] found blood phosphorus values which he considered high. He emphasized the fact that both osteopetrosis and chronic phosphorus poisoning are characterized by suppurative processes of the bones, and drew attention to the similarity in the two conditions of the transverse bands present in roentgenographs of the extremities.

Bernhardt [26] was unable to produce a negative calcium balance with doses of ammonium chloride, which, in his opinion, should have had this effect. He deduced that the tissues have an increased affinity for calcium, a concept which does not aid materially in understanding the disease. Flood [40] expressed surprise at the small quantity of calcium found in the urine of his patient in the presence of an elevated serum calcium concentration. He was also impressed with the quantity of parathyroid extract necessary to increase the urinary calcium excretion and to render the balance even moderately negative. Our own patient failed to respond in a characteristic fashion to doses of parathyroid extract, which might be expected to have produced a demonstrable effect. Although one approaches the interpretation of such results with the utmost caution and no small degree of skepticism, there are probably enough data to suggest that osteopetrosis may be accompanied by some sort of disturbance in the calcium and phosphorus metabolism. The nature of this disturbance, if present, is entirely conjectural. There is no way to determine, at present, whether it is related directly to the cause of the disease or whether it is simply an effect of the exaggerated production of bone. Laurell and Wallgren [13] found normal calcium metabolism in a well marked example of Albers-Schönberg's disease.

In animals a condition bearing some resemblance to the changes of bone in osteopetrosis can be produced by feeding a diet in which the phosphorus content is excessively high in relation to the calcium fraction. Strontium may at least partially replace phosphorus in such a diet with

60. Schulze, F.: Skelettveränderungen als Ursache von Verkalkungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **36**:243, 1923.

like results. The same is probably true of beryllium. Lehnerdt [61] was able to produce these changes in both fetuses and nurslings by feeding a diet containing strontium to the mother. Shipley, Park and their co-workers [62] subsequently drew attention to the fact that Lehnerdt's diets were high in phosphorus. However, there is nothing in the anamnestic data pertaining to Albers-Schönberg's disease to suggest that dietary peculiarities of a gross order have anything to do with the genesis of the syndrome. Although this detail does not seem to have been investigated exhaustively in all the reported cases, there is a rather uniform lack of evidence that osteopetrosis is based on environmental factors.

In the face, then, of contradictory anatomic findings with regard to the endocrine system and in the absence of convincing evidence pointing to environmental factors and deficiency, one is forced to the assumption that the fundamental pathologic changes in osteopetrosis lie within the osseous system itself. Blood and bone have the same primordial forerunners. Both arise ultimately from undifferentiated mesenchyme. When the primitive marrow cavity is formed, blood vessels grow in from the perichondrium, carrying with them an undifferentiated tissue which has within itself the potentiality of producing either hematogenic or osteogenic tissue. The most widely accepted current concept holds that the fundamental defect in Albers-Schönberg's disease consists in a faulty differentiation and development of this primitive substance. This expresses itself in the production of an excessive amount of abnormal osteogenic tissue which proliferates at the expense of, or in place of, normal blood-forming marrow. The marrow which develops is relatively fibrous and acellular, even in the presence of the demands made on it by severe anemia, and it is sometimes converted into bone by a process of metaplasia.

The familial and hereditary aspects of the disease and its common occurrence in utero are striking features. They have given rise to the hypothesis that the Albers-Schönberg syndrome results from a disturbance inherent in the germ plasm. Genetically this constitutes a mendelian recessive characteristic. The presence of the disease in the offspring is rendered more probable by the inbreeding of a strain characterized by this trait. Transmission is not sex-linked, and both males and females are affected equally. There is no evidence of racial predisposition.

In support of the assumption that osteopetrosis is a developmental disease one may adduce the example of osteopsathyrosis (osteogenesis

61. Lehnerdt, L.: Phosphorsklerose und Strontiumsklerose, Jahrb. f. Kinderh. **22**:395 and 610, 1910.

62. Shipley, P.; Park, E.; McCollum, E.; Simmonds, N., and Kinney, E.: Studies on Experimental Rickets: XX: Effect of Strontium Administration on Histological Structure of Growing Bone, Bull. Johns Hopkins Hosp. **33**:216, 1922.

imperfecta, fragilitas ossium, Lobstein's disease). Roentgenographically and pathologically this may be regarded as the diametric opposite of Albers-Schönberg's disease. The endosteal and perosteal production of bone is decreased, with the result that the cortex and the individual trabeculae are abnormally thin. The roentgen shadow of the bones is characterized by decreased opacity and reduced diameter. The growth in length is relatively unimpaired. The disease is both hereditary and familial; it may become recognizable either in utero or in childhood. Although etiologic investigations have been somewhat contradictory, accumulated evidence tends to show that osteopsathyrosis does not depend on primary disturbances in the calcium and phosphorus metabolism, endocrine changes or vitamin deficiency. Apparently it represents a fundamental anomaly of osteogenesis, the ultimate causes of which reside in the reproductive cells of the parents.

DIFFERENTIAL DIAGNOSIS

The fully developed syndrome consisting of pathologic fractures, roentgenographically opaque bones, retarded development, optic atrophy, anemia and enlargement of the lymphoid apparatus is not easily confused with any other disease. All cases, however, do not show the complete complex of symptoms described, and may lead to confusion in diagnosis. The possibility of error is greater when only a limited portion of the skeleton is included in the roentgen examination.

Chapman [63] recently reported two examples of osteosclerosis with anemia in adults. These were differentiated from Albers-Schönberg's disease by the absence of pathologic fractures and by the roentgenographic picture, in which the density of the bones was much less striking than it is in true osteopetrosis. Chapman investigated the possibility of silicosis as an etiologic factor, but was unable to come to a definite conclusion. He remarked that a similar disease has been observed in the Scandinavian peninsula, among workers in cryolite.[64]

It was stated in the introduction that disturbances in the architecture of bone in association with leukemia or pseudoleukemia were observed pathologically before Albers-Schönberg described the first case of osteopetrosis. This association is being recognized with increasing clarity from a clinical standpoint. Our own experience, however, and the published reports which we have been able to examine [65] serve to emphasize

63. Chapman, E. M.: Osteosclerotic Anaemia, Am. J. M. Sc. **185:**171, 1933.

64. Møller, P. F., and Gudjonsson, S. V.: Massive Fluorosis of Bones and Ligaments, Acta radiol **13:**269, 1932.

65. Poynton, F., and Lockwood, R.: Lymphatic Leukemia with Infiltration of the Periosteum Simulating Acute Rheumatism, Lancet **1:**1192, 1932. Smith, C. H.: Leukopenic Myeloid Leukemia Associated with Arthritis, Am. J. Dis. Child. **45:** 123 (Jan.) 1933.

that the roentgenographic features of the changes in bone in leukemia are essentially different from those in osteopetrosis. In leukemia the changes are predominantly infiltrative and destructive, there is much more involvement of the periosteum, the density attained is not so great, and the extent of the involvement probably never so universal as in Albers-Schönberg's disease. However, it is entirely possible that the increasing popularity of roentgenographic examination of the bones of leukemic patients will bring to light cases of a confusing nature. The myelophthisic blood picture described in terminal states of osteopetrosis does not differ markedly from the hematologic observations in certain cases of leukemia. In the present state of knowledge it is hardly possible to deny a fundamental relationship between the two entities.

There are numerous sclerosing diseases of bone, most of which have been found only in adults, and all of which show localization to a limited portion of the skeleton. This fact emphasizes the importance of complete examination of the skeleton when studying a difficult case. In the group are:

Condensing Osteitis of Sicard.[66]—This is characterized clinically by localized lumbocrural sciatic pain. It is sometimes associated with a neuritic type of muscular atrophy. Roentgenographically there is an increase in the density of the bones of the lumbar portion of the spine and pelvis without alteration in the outline of the affected parts. The condensation may appear in foci which are separate or contiguous and which fade imperceptibly into the adjacent normal bone. Constitutional and hematologic changes are lacking.

Eburnizing Osteitis of Putti.[67]—This is an entity characterized by the ivory-like density of a single bone, located usually in an extremity. There is some affinity for the region of the nutrient artery. No constitutional disturbances have been noted. A few observations of the same type of disease have been communicated by Froelich,[68] whose name is also attached to the condition.

Ivory Vertebra.—This was described by Souques, Lafourcade and Terris,[69] and is possibly related to eburnizing osteitis. It involves one or two of the vertebrae, producing a marked increase in the density. The etiology seems variable and obscure, but presumably it bears no relationship to Albers-Schönberg's disease.

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66. Sicard; Gally, and Haguenau: Ostéites condensantes coxales et vertébro-coxales, Rev. neurol. **1**:194, 1926. Bernard, P. M.: Etude clinique et radiologique des ostéites condensantes bénignues, Thèse de Paris, 1929.

67. Putti, V.: Una nuova sindrome osteopatica: L'osteosi eburneizzante monomelica, Chir. d. org. di movimento **11**:335, 1927.

68. Froelich: Quatre cas de tibias éburnés (Ostéose éburnante de Putti, ou os marmoréen des Allemands), Rev. d'orthop. **16**:1, 1929.

69. Souques; Lafourcade, and Terris: Vertèbre "d'ivoire" dans un cas de cancer métastatique de la colonne vertébrale, Rev. neurol. **1**:3, 1925.

Melorheostosis (*Monomelic Flowing Hyperostosis*).—This was first described by Léri,[70] and was reviewed recently by Moore and DeLorimier.[71] The latter regarded it as being related to Putti's disease. It consists in increased roentgenographic density and distortion of the outline of one or more bones in an extremity. When the disease involves more than one bone it does not spare the joint between, but "flows" through, producing characteristic changes therein. Roentgenograms give the impression that the bones are made of opaque wax which has been heated to the point of melting. This, too, is not a generalized disease from a roentgenographic standpoint.

In addition to the benign lesions, condensing alterations can be produced by neoplasm and infection. Cancerous metastases to bone are relatively rare in childhood, and the roentgenographic appearance of primary malignancy of bone is quite different from that of osteopetrosis. Of the infectious processes, congenital syphilis is the only one which is apt to cause confusion. It is noteworthy that one roentgenologist interpreted the films in our case as suggesting congenital syphilis. Characteristically, syphilis does not involve the base of the skull; it frequently produces destruction of bone and commonly affects the periosteum much more severely than does osteopetrosis.

Chronic poisoning with lead [72] and the protracted ingestion of phosphorus [73] are known to give rise to dense bands across the metaphyses of growing bone. A similar effect has been observed from the use of irradiated ergosterol. In addition, phosphorus poisoning may be associated with necrosis and suppuration of bone. In such cases a carefully taken history helps to prevent confusion.

Physiologic osteosclerosis of the new-born must be borne in mind. The skeleton of the newly born infant may present a degree of opacity which suggests a pathologic condition. This involves the whole skeleton, and may represent a physiologic storage of calcium. The increased density disappears in the course of the first few weeks. In cases of this sort differentiation must be made on nonroentgenographic data and on the basis of a follow-up examination at a later date.

Pathologic fractures may ensue from a large number of causes. The only other condition commonly seen by the pediatrician in which

70. Léri, A., and Joanny: Une affection non décrite des os: hyperostose "en coulée" sur toute la longuer d'un membre ou "mélorhéostose," Bull. et mém. Soc. méd. d. hôp. de Paris **46**:1141, 1922.

71. Moore, J., and DeLorimier, A.: Melorheostosis Léri: Review of the Literature and Report of a Case, Am. J. Roentgenol. **29**:161, 1933.

72. Caffey, J.: Clinical and Experimental Lead Poisoning: Some Roentgenologic and Anatomic Changes in Growing Bones, Radiology **17**:957, 1931.

73. Compere, F. L.: The Effect of Phosphorus in Rickets: I. The Roentgenologic Changes in Rickets Following Administration of Phosphorus, Am. J. Dis. Child. **40**:937 (Nov.) 1930.

there is a history of repeated fractures is osteogenesis imperfecta. In this condition the density of the bones is decreased rather than exaggerated, and there is marked interference with the growth in the diameter of the bones.

The combination of moderate hydrocephalus with optic atrophy may lead to confusion with primary pachymeningitis interna haemorrhagica unless the skeleton is examined by roentgen rays.

The large number of nucleated red cells in the blood smears may suggest familial erythroblastic anemia (Cooley) or a crisis in the course of familial hemolytic icterus. The well known roentgenologic aspects of Cooley's anemia need no comment. There have been no reports of altered fragility of the erythrocytes in Albers-Schönberg's disease, nor is the blood picture characterized by the presence of an abnormal number of microcytes.

The differentiation from leontiasis ossea should not be difficult, and there should be little confusion with respect to the typical or fully developed forms of Paget's disease or of osteitis fibrosa cystica. Hirsch,[74] however, emphasized the hereditary nature of fibrocystic disease of bone, and reported a family in which, of nine children, three were so affected. Bearing in mind the pleomorphic pathologic changes of osteitis fibrosa cystica, it is conceivable that incomplete examination of the skeleton might lead to confusion.

Several rare and unclassified conditions of bone have been reported. Some of these may be atypical examples of Albers-Schönberg's disease. However, because of the paucity of published data or the equivocal nature of the reproduced roentgenograms, it has seemed advisable to relegate them to this section.

Voorhoeve[75] reported a familial dystrophy of bone characterized by the presence of alternating striations of greater and less density arranged longitudinally in the extremities and in a fan-shaped fashion in the bones of the pelvis. There were three cases in the author's family, in father, son and daughter. Some writers have related this syndrome to Albers-Schönberg's disease, although the evidence for such classification is not stated.

Lauterburg[76] reported the case of a father and son who showed generalized roentgenographic sclerosis of bone together with certain physical peculiarities. He did not believe that these were cases of true osteopetrosis because of the striking involvement of the middle phalanges

74. Hirsch, S.: Is Generalized Osteitis Fibrosa (Paget and von Recklinghausen) Congenital? Am. J. Surg. **3**:167, 1927.

75. Voorhoeve, N.: L'image radiologique non encore décrite d'une anomalie du squelette, Acta radiol. **3**:407, 1924.

76. Lauterburg, W.: Ueber Zwei Fälle von familiärer generalisierter Osteosklerose, Deutsche Ztschr. f. Chir. **230**:308, 1931.

of the hands, which were also enlarged and deformed. Furthermore, there was no history of pathologic fracture, and no change in the blood picture. He felt that the peculiar physical development pointed to some sort of endocrine disturbance.

Camurati [77] published rather meager data concerning a painful affliction of the lower extremities in a father and son whom he saw. From historical data he concluded that the same disease had been present in several members of the father's family through four generations. He reproduced roentgenograms of the lower extremities of both father and child. The changes in the son are difficult to evaluate, but the femurs, tibias and fibulas in the father are roentgenographically typical of Albers-Schönberg's disease. The Wassermann reaction was negative in both cases. From the facts available we are unable to classify these cases.

Engelmann [78] described a case which may bear some relationship to osteopetrosis, a possibility which Péhu was inclined to favor. His patient was a boy of 8 years who showed mild anemia and osteopathy characterized by increased density of the shafts of the long bones and the base of the skull. The ends of the shafts and the epiphyses were not involved. The hands, feet and pelvis were normal. The roentgenographs suggest that this may be an arrested case of Albers-Schönberg's disease. This possibility is entirely conjectural, and the case remains unclassified.

The roentgenographic appearance of the bones in the familial osseous dystrophy which Kemkes [79] reported suggests strongly that the etiologic factor lay in the phosphorized cod liver oil which the patients had received. The author, however, felt that this possibility could be excluded, and related the process to endocrine disturbances.

PROGNOSIS

The prognosis for osteopetrosis seems related directly to the severity of the manifestations and this in turn to the age at which the disease becomes clinically obvious. Those in whom the condition develops in utero and who present the complete clinical picture at the time of birth or within the first few months of life apparently survive for a relatively short time. The large number of miscarriages, stillbirths and deaths in infancy which has been recorded in the families of patients with osteopetrosis suggests that the mortality in the infantile type of

77. Camurati, M.: Di un raro caso di osteite simmetrica ereditaria degli arti inferiori, Chir. d. org. di movimento **6**:662, 1922.

78. Engelmann, G.: Ein Fall von Osteopathia hyperostotica (sclerotisans) multiplex infantilis, Fortschr. a. d. Geb. d. Röntgenstrahlen **39**:1101, 1929.

79. Kemkes, B.: Ueber familiär auftretende Störungen des Knochenwachstums im Röntgenbilde, Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:90, 1929.

case is high. The patients who do not have hydrocephalus have a better outlook than do those so stigmatized. Those whose sole symptom has been pathologic fractures and in whom the disease has been discovered incidentally by roentgen examination seem to have done moderately well. We have insufficient information to determine whether or not the disease is invariably progressive. Albers-Schönberg's case is the only one in which the details of protracted observation have been published. This patient died of progressive anemia. The possibility of spontaneous arrest of the disease or regression of the lesions is still to be investigated.

The impairment of activity is conditioned by the severity of the anemia, the number of fractures and the rapidity with which they heal. As has been stated, these usually heal well although in individual instances union has been delayed. In general the mentality is unimpaired.

Death results from intercurrent infection or anemia. In some cases the former emanates from the foci of suppuration common to the disease.

TREATMENT

No form of beneficial therapy has been suggested. Lorey and Reye [32] recorded failure with the use of pituitary extract. Kopyloff and Runowa [35] felt that their patient was injured rather than benefited by treatment with ultraviolet rays. Measures which tend to increase the calcification of bone are said to be contraindicated on purely theoretical grounds. On the same premises one might urge the use of agents which are known to lower the retention of calcium, such as mineral acid ions and parathyroid extract. It may be recalled that Bernhardt [26] noted some subjective betterment and slight improvement in the blood picture in association with the administration of ammonium chloride. However, since the condition probably is one of abnormality of histogenesis rather than of the calcification of bone, it is difficult to see what benefit would accrue from decalcification alone. Such measures could hardly be expected to influence the blood-forming organs. Under the impression that they were dealing with hyperparathyroidism, Péhu, Policard and Dufourt [18a] suggested the removal of parathyroid tissue. There is little support of their point of view in the available postmortem material other than the presence of calcium deposits in the subcutaneous tissues in the case reported by Schulze.[30] The parathyroid bodies were structurally normal in this case. The four metabolic studies which have been performed are against this etiology. Yet the knowledge of the possible disturbances of the parathyroids is so incomplete that parathyroidectomy cannot be summarily rejected.

The treatment of the fractures is an orthopedic problem. In several cases it has been necessary to resort to open reduction with the use of bone plates. Reduction of the fracture may be complicated by the presence of osteomyelitis at the site of the lesion.

There are no data regarding the influence of liver and iron on the blood picture. From general experience with this type of anemia it is not likely that the condition would be benefited by anything short of transfusion. Because of occasional reports of compensatory hematopoiesis in the spleen, removal of that organ is said to be contraindicated. Frank's [31] patient was neither benefited nor harmed by splenectomy.

For obvious reasons many authors recommend the proscription of consanguineous marriages and the prevention of offspring in families in which a case has occurred. The last suggestion seems debatable, since not all children in such families manifest the disease.

SUMMARY AND CONCLUSIONS

1. The literature of osteopetrosis (Albers-Schönberg's disease) has been reviewed, and a summary is presented of its historical, anatomic, chemical and clinical aspects. The cases which have been diagnosed and reported up to 1933 are tabulated.

2. A new case of the disease is presented, with metabolic and hematologic data.

3. There is no evidence at the present time to suggest that osteopetrosis is due to endocrine disturbance, environmental factors, dietary deficiency or chemical poisoning. Although it is possible that there are inconstant associated changes in the calcium and phosphorus metabolism, these alterations, if present, are probably secondary manifestations of a primary disturbance in the formation of bone. The Albers-Schönberg syndrome is a true developmental disease which consists in faulty differentiation of the primitive common forerunner of osteogenic and hematogenic tissue. The ultimate cause of the abnormality is unknown, but it seems to be a property of the parental germ plasm.

NOTE.—Since this review was accepted for publication the following reports of cases of Albers-Schönberg's disease have come to our attention. The data on these cases have not been included in our analysis.

Case 66.[80]—The patient was a male Italian infant, 3 months old. He died before the end of the first year of life. No anatomic examinations were made. The blood was studied carefully by hematologic methods and somewhat less exhaustively from a chemical standpoint.

Case 67.[81]—The patient was a female infant, 10 months old, of Italian parentage. She was alive at the time of the report of her case, thirteen months after the first examination. No pathologic data had been obtained. Complete roentgenographic studies were reported, together with hematologic examinations and blood chemistry.

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80. Guassardo, G.: Un caso di "morbo marmoreo" (Studio clinico, radiologico ed ematologico), Riv. di clin. pediat. **30**:1531, 1932.

81. Robertson, G. E.: Congenital Osteosclerosis, J. Pediat. **3**:439, 1933.

SUBACUTE PERIBRONCHIOLAR PNEUMONIA

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During the past five years we have had the opportunity of observing in infants a form of respiratory disease the distinctive clinical and pathologic features of which constitute in our opinion a definite entity.

American and English textbooks on pediatrics have given no serious consideration to the clinical and pathologic picture to be described and discussed here. Did we not know from our own work that it is seen rather frequently in the United States, we might imagine that it was peculiar to the continent of Europe, and particularly to Germany where excellent descriptions have appeared in several different textbooks. In 1906 Heubner [1] presented the subject in detail, both from the clinical and from the pathologic standpoint, in his usual clear and convincing manner. Strümpel [2] and Pirquet [3] also described the picture. However, even from the presentations of these authors one does not receive the impression that the disease is relatively common in infants. Since this is the conclusion to which we have come on the basis of our experience in the Babies and Childrens Hospital we have considered it worth while to present our clinical and pathologic observations on subacute peribronchiolar pneumonia.

For the eight patients who have come to autopsy the clinical diagnosis was verified by the demonstration of respiratory obstruction due to subacute or chronic inflammation of the bronchioles. These pathologic changes have been described repeatedly in pneumonia following contagious diseases but never, except by the aforementioned authors, as a primary independent disease.

SIGNS AND SYMPTOMS

Subacute peribronchiolar pneumonia is a disease of infants.

This disease exhibits the following cardinal signs and symptoms: (1) a persistent cough which is productive, paroxysmal and extremely

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1. Heubner, O.: Lehrbuch der Kinderheilkunde, ed. 2, Leipzig, Johann Ambrosius Barth, 1906, vol. 2, p. 242; ed. 3, 1911, vol. 2, p. 271.

2. Strümpel, A., in Seyfarth, C.: Lehrbuch der speziellen Pathologie und Therapie der inneren Krankheiten, ed. 26, Leipzig, F. C. W. Vogel, 1927, vol. 1, p. 272.

3. Pirquet, C.: Krankheiten der Respirationsorgane, in Feer, E.: Lehrbuch der Kinderheilkunde, ed. 8, Jena, Gustav Fischer, 1922, p. 332.

debilitating; (2) an absolute increase in the volume of the lung due to a generalized emphysema; (3) the presence of fine râles which are heard more or less constantly, at times diffusely throughout the chest and at times localized and migratory; (4) inspiratory retractions of the epigastrium, intercostal spaces and suprasternal notch; (5) a history of a progressive respiratory ailment of at least four weeks' duration, associated with cough, cyanosis, pallor and dyspnea.

The fourteen patients included in this study were children under 2 years of age, and in all the first symptoms had developed before the end of the first year; in fact five had coughed since birth. The onset may apparently be innocent of any grave import. What appears to be a common infection of the upper respiratory tract may gradually show the pathognomonic signs and symptoms of bronchiolar obstruction. Sometimes repeated "colds" occur before the graver picture appears. However, in just as many cases the entire syndrome of obvious respiratory infection with emphysema, bronchiolar obstruction and cyanosis develops acutely within a few days. Apparently the mode of onset bears no relation either to the duration of the disease or to the ultimate prognosis.

At the acme of the disease the patients are alert and apprehensive. Fearful of any alteration in their tense attitude they ward off every exertion, even swallowing, which might produce the dreaded cough. Cyanosis which is usually visible at all times around the lips and nail beds, may on exertion involve the entire body. A slight cough may accompany each expiration, or it may come only in paroxysms, in the latter event resembling the seizures of pertussis. The children are usually underweight because of the difficulty in feeding. The chest is often deformed, having either the barrel shape or a Harrison's groove with the persistent vertebral retraction of the xiphoid process characteristic of "shoemaker's chest." The emphysema is so great that it obscures cardiac and hepatic dulness and, because of the descent of the diaphragm, displaces the liver. As the diaphragm descends, its arc decreases and its efficiency as a muscular organ increases.[4] It overcomes the force exerted by the intercostal movement, decreasing the normal lateral and ventral movement of the costal margins and finally producing a mesial and dorsal retraction. In addition, the loss of extensibility of the pulmonary tissue, induced by the bronchiolar obstruction and the interstitial inflammation, leads to retractions of the xiphoid processes and of the tissues in the suprasternal notch and supraclavicular and intercostal spaces. The breath sounds are long and labored and may be very faint. The fine crepitations which accompany the breath sounds may in some cases be innumerable and constant while

4. Hoover, C. F.: The Diagnostic Significance of Inspiratory Movements of the Costal Margins, Am. J. M. Sc. **159**:633, 1920.

in others they are inconstant and focal. Repeated examinations should, however, reveal these fleeting râles at some time in all parts of the chest. In the throat a mucopurulent secretion collects which further impedes respiration. The dyspnea increases; the children attempt to refuse nourishment and in utter exhaustion are capable of only a faint whine.

This disease has no characteristic curve for temperature. A normal or slightly elevated temperature is present at irregular intervals. Higher degrees of fever are seen in cases of longer duration, and the temperature frequently sinks to subnormal levels just before death.

COMPLICATIONS

The postmortem examination shows that peribronchial and peribronchiolar pneumonia is an invariable and essential feature of the disease. On the other hand, the diffuse pneumonias which are recognizable by physical examination occur relatively late and are usually the precursors of death. They may appear as small patches which coalesce gradually, or an entire lobe may suddenly become atelectatic and then pneumonic. Sinusitis and otitis media are common complications. Parenteral dyspepsia is frequently seen. Edema developed in five patients. This was probably not due to a disease of the kidney since the urines were normal and in one case a careful examination of the renal function showed no impairment. Furthermore there was no vascular collapse or cardiac decompensation. In one case the serum protein was determined. It was 7.46 per cent.

PROGNOSIS

The prognosis is poor. Twelve children died after an illness of from one to eighteen months. Two children, aged 7 weeks and 8 months, respectively, presented a picture very similar to that which we have described; their condition remained unchanged for two months and one month, respectively, and then improved. At the time of discharge from the hospital one of the infants still showed a few scattered râles and a retraction of the lateral costal margins on quiet inspiration. The ultimate issue in these two cases is still doubtful because some of the children who died had periods of temporary improvement. The white cell count is not characteristic, ranging usually from 10,000 to 20,000, although in a few instances higher counts occurred shortly before death when diffuse pneumonia was present. The polymorphonuclear type of cell predominates. A lymphocytic response may occur, however, as is the case in other acute infections in infants.

ROENTGENOLOGIC FINDINGS

The roentgenogram may show no changes other than those indicative of emphysema. The pulmonary fields are dark; the ribs are usually in

a position of extreme inspiration, and the arc of the diaphragm is depressed and flattened. The hilar shadows and the pulmonary markings may be increased in intensity, a finding which may be characteristic of nothing more than a bronchitis. The markings are particularly dense about the cardiac shadow. In two instances there were dense shadows at the right cardiac border which postmortem examination revealed in one case to be due to an atelectatic middle lobe of the right lung and in the other to interlobar pleurisy. Early stages of the disease, however, are characterized by relatively slight roentgenologic findings in the face of serious pulmonary signs and symptoms.

PATHOLOGIC CHANGES

Autopsies were performed in eight of twelve fatal cases.

Pathologic Examination.—In three cases entire lobes of the lungs were dehydrated, cleared in cedarwood oil and studied with a binocular lens. The tissue was subsequently embedded and sectioned for microscopic study (fig. 1). Routine hematoxylin and eosin, and Gram's [5] and Saphir's orcein stains were used on sections from many blocks of all the lungs. Blocks from the lungs of four patients were sectioned serially and stained with hematoxylin and eosin or with Saphir's [6] orcein. Foot's [7] silver carbonate stain and a combination of Masson's [8] trichrome light green and Verhoeff's [9] elastic stains were used for the identification of reticulum, elastic fibrils and smooth muscle.

The lungs were characteristically voluminous and covered the anterior surface of the heart. The arch of the diaphragm was flattened. Emphysematous marginal bullae were seen occasionally. Although interlobar adhesions were common and the visceral pleura was thickened over large areas, adhesions between the visceral and parietal pleural surfaces were unusual. In a few cases thin patches of fibrin were seen distributed irregularly over the visceral surfaces and were usually related to underlying consolidation. Although the lungs were generally distended there were areas of atelectasis and bronchopneumonic consolidation. Such atelectatic portions were generally peripheral, often paravertebral and tended to be of lobular distribution. In a few instances all or a large portion of one lobe was collapsed. Exudate could usually be scraped from atelectatic portions of the lung. The relative amount of atelectasis varied and was generally greater in the cases in which the disease had been of longer duration. Extensive pneumonic consolidation was not a prominent feature of the disease.

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5. The formula for Gram's staining method may be obtained from Conn, H. J.; Mallory, F. B., and Parker, Frederic, Jr., in McClung, C. E.: Handbook of Microscopical Technique, New York, Paul B. Hoeber, Inc., 1929.

6. Saphir, O.: Involvement of Medium-Sized Arteries Associated with Syphilitic Aortitis, Am. J. Path. **5**:397, 1929.

7. Foot, N. C., and Mènard, M. C.: A Rapid Method for the Silver Impregnation of Reticulum, Arch. Path. **4**:211 (Aug.) 1927.

8. Masson, P.: Trichrome Stainings and Their Preliminary Technique, J. Tech. Methods **12**:75, 1929.

9. The formula for Verhoeff's elastic stain may be obtained from Conn, Mallory and Parker.[5]

Fig. 1.—Upper and lower lobes of a lung that is the seat of subacute bronchitis, bronchiolitis and peribronchiolar pneumonia. The inflammation is most pronounced in the small bronchi and bronchioles with dilatation and obstruction by exudate. The entire lung is distended; actual size.

Small shotlike nodules could be palpated, especially in the peripheral portions of the lungs. These masses measured from 2 to 5 mm. in diameter and were usually separated from the pleura by air-containing tissue. They were firm, pale, rounded and fleshy and projected slightly above the cut surface. In the center of most of these indurated areas a dilated air passage filled with thick, viscid gray or yellow pus could be recognized. In comparison with the inflammation of the smaller air passages, larger bronchi were relatively uninvolved. Pus was found in some, but the trachea and primary bronchi were usually free from exudate, and the mucosa was often unaltered.

Microscopically the most outstanding change was the bronchiolar and peribronchiolar inflammation. The changes were most uniform and least complicated

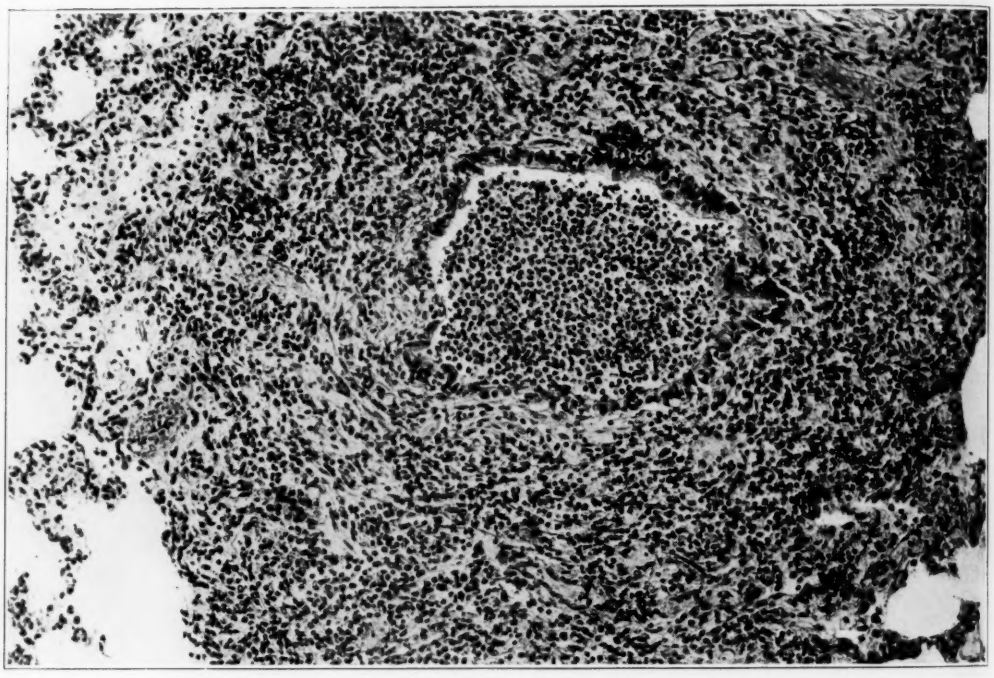

Fig. 2.—Typical bronchiolitis and peribronchiolar pneumonia; × 120.

by lobular pneumonia in the cases in which the disease was of shorter duration. Even in these, however, the variation in the type of involvement was such as to require serial sections or sections large enough to include most of a lobe in order to correlate the changes in an air passage with those in its connected alveoli.

The acute phase of the inflammation was an exudative bronchitis and bronchiolitis which was most prominent in the small bronchi and bronchioles where the diameter of the passages was small enough to permit their obstruction either by exudate or by edema of the mucosa (fig. 2). Neither the mucosal swelling nor the amount of exudate was great enough to obstruct the larger bronchi, and in many instances inflammation in them was minimal or entirely absent. The obstructing plugs of exudate usually ended in the respiratory bronchioles. Beyond them the alveolar ducts and alveolar sacs were free from exudate and were distended by

entrapped air as indicated by the concave surface of the obstructing exudate (fig. 3). Thus the mucosa was the seat of acute, nonalterative inflammation, which produced an accumulation of fibrinopurulent exudate in the lumen of the passage and varying degrees of mucosal edema. The mucosal swelling was usually concentric, but in places the lumen was rendered eccentric by focal aggregations of exudative cells and fibrin beneath the epithelium (fig. 4). It was not uncommon to encounter partially or completely encircling ulceration of the mucosa, leaving remnants of the musculo-elastic layer to mark the site of the lumen.

What appeared to be the direct sequel to this acute mucosal inflammation was the extension of the process through the walls of many of the small bronchi and

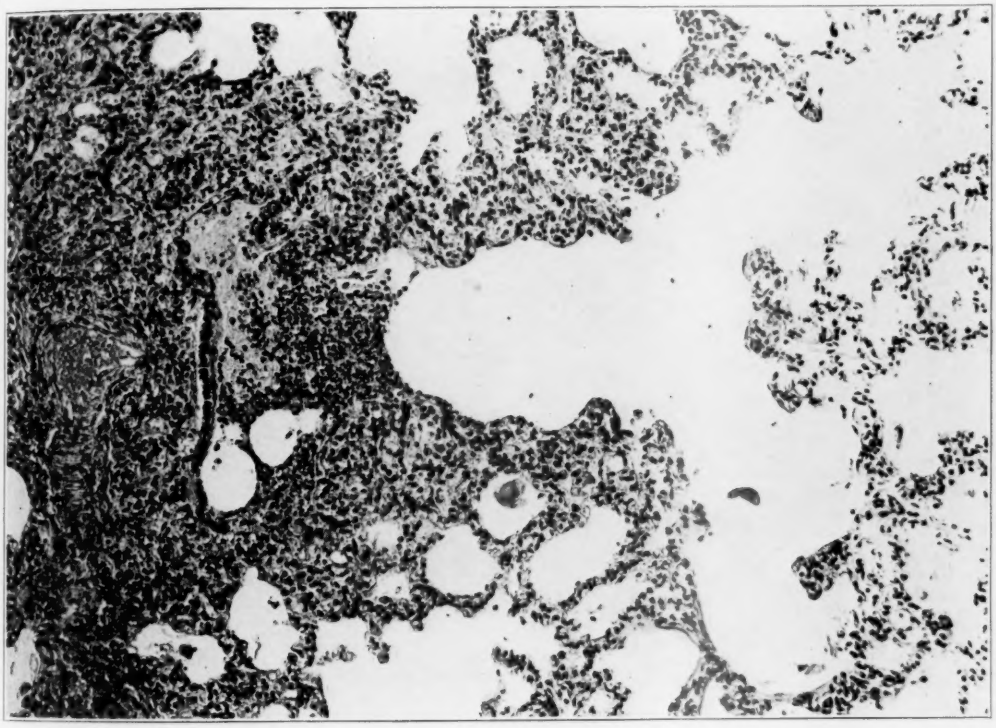

Fig. 3.—Bronchiole obstructed by fibrinopurulent exudate with distention of alveolar ducts distal to the obstruction. Note the concave surface of the exudate; × 100.

bronchioles. The fibrinopurulent exudate penetrated not only through the entire thickness of the bronchiolar wall but even into the interstitial tissue and adjacent alveoli so as to form a peribronchial or peribronchiolar collar of consolidation (fig. 2). The nodular character of the consolidation was in reality due to a series of local circumferential expansions of peribronchial and peribronchiolar penumonia which, as was demonstrated by serial sections and large cleared preparations of lung, possessed a branching and irregularly cylindric form. This pneumonia, extending from bronchioles to adjacent alveoli by contiguity, was essentially a subacute, fibrinopurulent, productive inflammation. The development of pneumonia by

continuity along the bronchiolar epithelium and into the distal air sacs was seen more especially in atelectatic portions of the lungs, and this pneumonia was for the most part lobular. Although in a few cases many lobules were consolidated in this manner, this condition was not characteristic of the disease.

The proliferative changes in the mucosa of the small air passages varied considerably. In some situations there was hyperplasia of the superficial epithelium forming a pseudostratified layer several cells deep. The innermost layer usually remained ciliated, but this was not invariably true. Another progressive change lay in the organization of exudate within the air passage so as to form a partial

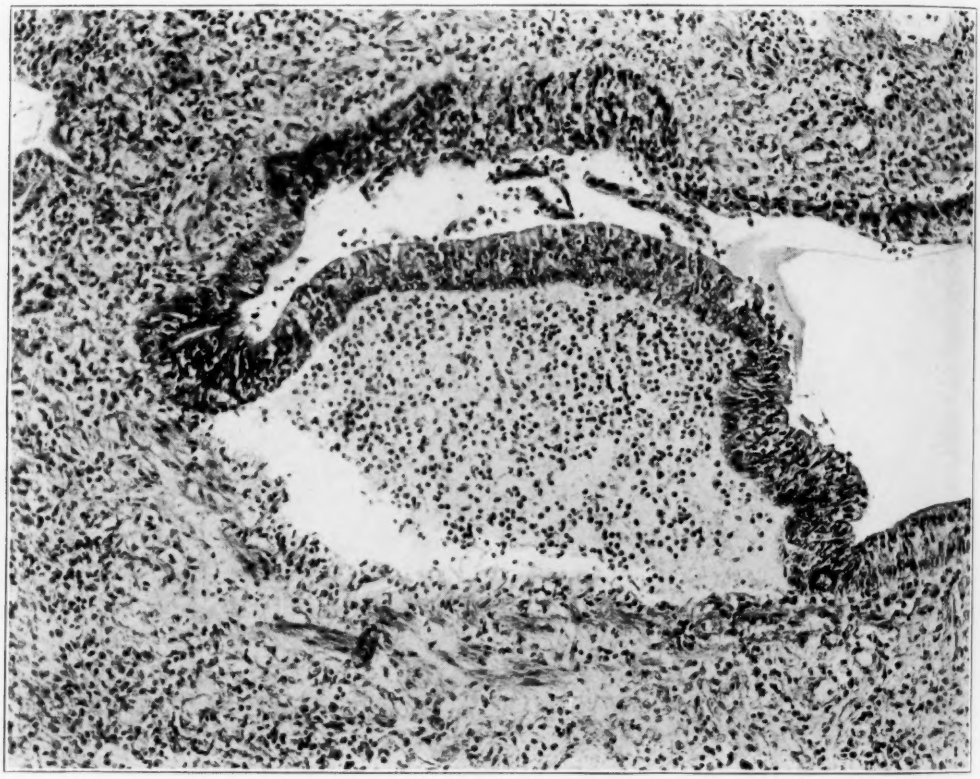

Fig. 4.—Bronchiolar obstruction by subepithelial collection of exudate; × 130.

or completely obstructive mass of granulation tissue (fig. 5). The lobules in which such an obliterative bronchiolitis had occurred were atelectatic and frequently fibrous and atrophic. In such areas single lobules bore a superficial resemblance to those seen in pneumonia alba. Such a lobule was sharply defined by thickened interlobular septums, and the alveoli were partially or completely obliterated by fibrous thickening of their septums. Air sacs which remained patent were filled with desquamated alveolar cells and mononuclear phagocytes.

The character of the exudate varied considerably in the various bronchioles affected. The characteristic type of exudate was fibrinopurulent, but with organization and resolution the fibrin became less conspicuous and the cells predominantly

mononuclear phagocytes. Giant cells were more commonly seen in the late phases of the process, but they were never conspicuous. Two types were present, the fused alveolar lining cells and the multinucleated phagocytes.[10] Neither cytoplasmic nor nuclear inclusion bodies were found.

Hyperplasia of mediastinal lymph nodes was a constant and prominent observation. Frequently the peribronchial nodes formed nodular masses varying from 2 to 3 cm. in diameter. Histologically, these nodes were the seat of an acute hyperplasia without necrosis or fibrosis.

Cardiac hypertrophy was present in four of the eight infants on whom autopsies were performed. The weights of the heart were increased from 30 to 70 per cent

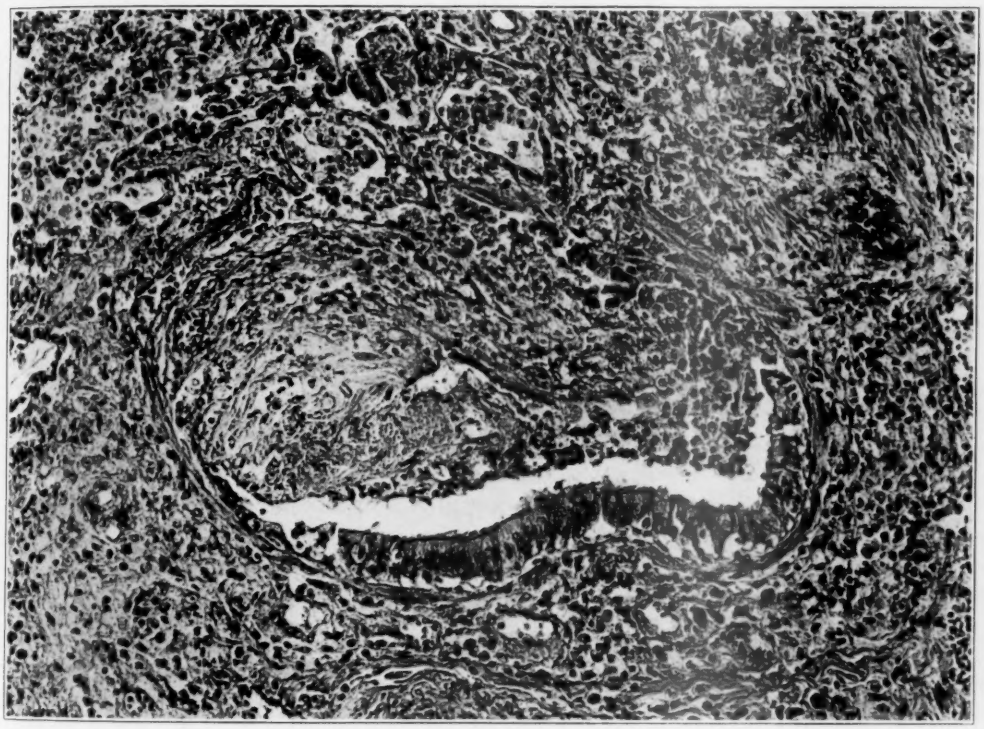

Fig. 5.—Organization of intrabronchiolar exudate with partial obstruction and organizing peribronchiolar pneumonia; × 195.

over the mean for the respective ages according to the figures of Scammon.[11] The hypertrophy was principally confined to the right ventricle and corresponded to the clinical finding of an increase in the area of right cardiac dulness. An electrocardiogram obtained of one of these patients revealed a right ventricular preponderance.

10. Moore, R. A., and Gross, P.: Giant Cells in Inflammations of the Lung in Children, Am. J. Dis. Child. **40**:247 (Aug.) 1930.

11. Scammon, R. E., in White House Conference on Child Health and Protection: Growth and Development of the Child, pt. 2, Anatomy and Physiology, Section I A, New York, Century Company, 1933, p. 262.

The spleen was frequently the seat of an acute hyperplasia, and the liver, spleen and kidneys commonly revealed passive hyperemia of varying intensity.

SUMMARY OF GROSS AND MICROSCOPIC PATHOLOGIC CHANGES

The postmortem examinations of the eight children showed subacute and chronic bronchiolitis, peribronchiolar pneumonia, bronchiolectasis and emphysema. The bronchiolitis was obstructive by reason of either mucosal swelling and intrabronchiolar exudate or organization of intrabronchiolar exudate with consequent obliteration. During the more acute phase of the inflammation in a given bronchiole the process was destructive and exudative, with especially severe damage to the musculoelastic elements of the walls of small air passages and resulting ectasia. In the later stages of the inflammation the process was productive with resulting peribronchiolar induration. Concomitant with the obstruction of air passages, peripheral distention, emphysema and atelectasis developed. The relative proportions of emphysema and atelectasis appeared to depend on the completeness and duration of the bronchiolar obstruction. Emphysema, however, was characteristically predominant.

DIFFERENTIAL DIAGNOSIS

The characteristic history of repeated or continuous respiratory infection, the irritating, productive and exhausting cough, the signs of bronchiolar obstruction and the generalized nature of the lesion form a syndrome which should not be mistaken for common bronchopneumonia. The cases of chronic migratory pneumonia, often erroneously called unresolved pneumonia, which we have studied both during life and at autopsy, did not show these cardinal signs and symptoms. Chronic pneumonia in young infants, particularly when associated with much atelectasis, may confuse the observer, since the chest of the child at this age is pliable and yields to the pull of the diaphragm and accessory muscles of respiration when the extensibility of the pulmonary tissue has been decreased by inflammation. Thus bronchiolar obstruction may be simulated, especially since some complementary emphysema usually occurs in response to the atelectasis accompanying bronchopneumonia.[12] In such cases, however, we have not observed the characteristic paroxysmal cough or the purulent secretion in the throat which is so frequent and plentiful in subacute peribronchiolar pneumonia.

Foreign bodies may produce diffuse bronchial disease, but the obstructive lesions are usually confined to one side of the thorax. Moreover, foreign bodies are rarely found in the lung during the first year of life. Another exceedingly rare disease which must be con-

12. Karsner, H. T.: Human Pathology, ed. 3, Philadelphia, J. B. Lippincott Company, 1931, p. 12.

sidered in the differential diagnosis, bronchiolitis fibrinosa, is recognized by the typical casts which are expectorated by the patient.

McGillicuddy[13] recently described a case of acute generalized bronchiolectasis with bullous emphysema. The disease was first recognized by Sharkey,[14] and cases were subsequently reported by Ewart,[15] Emery and Langmead [16] and Barlow.[17] It is characterized by a rapid onset and equally rapid course, quite in contradistinction to the syndrome we have described. The pathologic anatomy is entirely different. At autopsy acute generalized bronchiolectasis presents innumerable cystic cavities which are apparently produced by an expansion and subsequent coalescence of alveoli.

A more serious problem in the differential diagnosis of subacute peribronchiolar pneumonia is pertussis. This possibility was given serious consideration in all the cases described in this report. There were no sources of this infection, and although the patients were kept in the general ward, no case of pertussis ever developed. The paroxysmal cough was never accompanied by a reprise, and it increased in intensity with the advance of the pulmonary disease. This is in contradistinction to the cough of pertussis which tends to become modified and in fact may disappear after the onset of pneumonia. Moreover, the histories of our patients did not reveal a period of cough preceding the pulmonary disease. In fact the most consistent feature in the onset of this disease is the history of a severe "cold" followed by cough, dyspnea, cyanosis and related symptoms.

COMMENT

The histopathologic changes revealed by these cases indicate that the disease is initiated by a fibrinopurulent bronchitis and bronchiolitis. Whether this primary inflammation affects the bronchial tree diffusely or focally cannot be determined with certainty. It might be supposed that the panbronchiolitis seen in these cases is the end-stage of a progressive acute capillary bronchitis. This was apparently Heubner's opinion. In some of the cases the history describes an acute onset with all the characteristic signs and symptoms. In these patients therefore originally there might well have been an acute diffuse disease of the

13. McGillicuddy, O.: Acute Generalized Bronchiolectasis with Bullous Emphysema, Ann. Otol., Rhin. & Laryng. **40**:1146 (Dec.) 1931.

14. Sharkey, S.: Acute Bronchiectasis, St. Thomas' Hosp. Rep. **22**:33, 1892.

15. Ewart, W.: Bronchial Dilatation: Bronchiectasis and Bronchiolectasis, in Albutt, C., and Rolleston, H. D.: A System of Medicine, London, The Macmillan Company, 1909, vol. 5, p. 127.

16. Emery, W. D'E., and Langmead, F. S.: Bronchiolectasis, Clin. J. **36**:79, 1910.

17. Barlow, D. L.: Extensive Bronchiolectasis in a Young Child, M. J. Australia **1**:99 (Jan. 27) 1923.

bronchioles. In others, however, the onset was gradual, and exacerbations followed one another over weeks or months before the typical picture appeared. Moreover, if the inflammation was diffuse at the onset, it certainly did not progress uniformly in all parts of the lung. Although the inflammation as seen at the time of autopsy was preponderantly subacute, various portions of the same lung frequently showed acute, subacute and chronic changes. This corresponds to the migratory character of the signs observed during life.

The localization of the inflammation in and around the small air passages with subsequent subacute and chronic changes is probably explainable by a mechanical cause. It can be assumed that the most important means of defense against injury to air passages are the ciliary movement and the cough reflex. This clearing of the passages is obviously rendered more difficult when the intrabronchiolar exudate is rich in fibrin, as was the case in the lungs included in this study. The large amount of fibrin in the exudate tends to reduce its fluidity and to facilitate its fixation to the mucosa, the relative surface size of which is greater in the smaller air passages than in the larger bronchi. Plugs of exudate, containing large numbers of bacteria and fixed in the lumens of bronchioles, were often found, whereas the larger bronchi remained relatively free from exudate. The continued activity of the inflammation with the development of subacute and chronic changes in and around small air passages was in all likelihood attributable to obstruction by this infectious material. In some instances the organization of the exudate within bronchioles leads to an obliteration of the air passage, a condition which was never seen in the larger radicles.

It does not, however, appear that obstruction by the unorganized exudate was functionally complete since emphysema predominated over atelectasis. The lobules of completely obstructed air passages would not retain air. It seems likely that the ball valve action of a partially obstructing exudate led to the distention so commonly seen. In order, therefore, to explain the increased volume of the lung in cases of partial bronchiolar obstruction it is necessary to assume that the pressures created in the bronchial system by inspiration are greater than those created by expiration. The experimental investigation of this problem has been undertaken by Thornton and Pratt [18] and by Hartwich.[19] In our cases the air content of lobules in the same lobe often varied, some being merely distended with air, while in others there had been a rupture of the septums and coalescence of alveoli. Atelectasis apparently denoted more complete bronchiolar obstruction and was lobar

18. Thornton, W. L., and Pratt, J. P.: The Relation of Bronchial Stenosis to Bronchiectasis, Bull. Johns Hopkins Hosp. **19**:230, 1908.

19. Hartwich, A.: Das Pneumotachogramm bei einigen Erkrankungen der Lunge und Luftwege, Klin. Wchnschr. **8**:1902 (Oct. 8) 1929.

in a few instances. More often it was lobular, and the atelectatic lobules were commonly the seat of a bronchopneumonia which had been produced by direct extension of the inflammation within the air passages. The most striking atelectasis was seen when bronchiolar obliteration was present; it was characterized by lobular atrophy and fibrosis. Bronchiolar obliteration similar to that observed by us was recently described by Nutting [20] in the report of a case of "capillary bronchitis."

Although the disease observed in these cases was apparently primary and in no sense a postinfectious pulmonary inflammation, the changes were essentially the same as those described in the so-called "measles pneumonia." In a detailed study of this pulmonary disease, Feyrter [21] has described a series of cases presenting essentially the same pathologic changes as those observed in this series. This particular type of bronchiolitis and peribronchiolar pneumonia has also been studied in detail and the literature reviewed by Hart,[22] Lauche [23] and Loeschcke,[24] all of whom classify it as a postinfectious process most commonly seen during or after measles, but also complicating or following pertussis and influenza.

Consideration must be given to the possible significance of bronchiectasis in the pathogenesis of the disease. The studies of Piltz [25] and of Wiese [26] have indicated that in most instances bronchiectasis should be regarded as a result of peribronchial and interstitial pulmonary inflammation. Wiese believes that congenital bronchiectasis is exceedingly rare and that acquired bronchiectasis is prone to follow any long-standing pneumonia in childhood. He does not, however, exclude the possibility of some inherent weakness in the walls of bronchi and bronchioles which might make the ectasia more marked in some patients than in others. Piltz also believes that the ectasia is the direct result of damage caused by inflammation of the bronchi. In the lungs studied in our investigation there was microscopic evidence of destruction of the

20. Nutting, R. E.: Capillary Bronchitis: The Effect of the Administration of Oxygen on the Healing Process, Am. J. Dis. Child. **37**:1051 (May) 1929.

21. Feyrter, F.: Ueber die Masernpneumonie, Virchows Arch. f. path. Anat. **255**:753, 1925.

22. Hart, C.: Anatomische Untersuchungen über die bei Masern vorkommenden Lungenerkrankungen, Deutsches Arch. f. klin. Med. **79**:108, 1903.

23. Lauche, A.: Die Entzündungen der Lunge und des Brustfelles, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, p. 701.

24. Loeschcke, H.: Die Pathologie der Kinderpneumonien, Monatschr. f. Kinderh. **41**:135, 1928.

25. Piltz, G.: Beitrag zur Kenntnis der Bronchiektasie im Kindesalter, Monatschr. f. Kinderh. **22**:551, 1922.

26. Wiese, O.: Die Bronchiektasien im Kindesalter, Berlin, Julius Springer, 1925 (forms vol. 2, Beihefte z. Beitr. z. Klin. d. Tuberk., 1927).

musculo-elastic elements of the walls of small air passages as a direct result of the inflammation. The finding of dilated bronchioles not the seat of inflammation does not require the hypothesis of a congenital anomaly, as the migratory character of the disease would account for damage to bronchioles no longer the seat of active inflammation.

The etiology of subacute peribronchiolar pneumonia cannot be settled on the basis of our present information. Bacteriologic studies of the cases during life showed the presence of staphylococci, streptococci, pneumococci, Bacillus influenzae and Micrococcus catarrhalis in the pharyngeal and bronchial secretions. The cultures made post mortem from blood and pulmonary tissue were equally inconclusive since many organisms of the common respiratory flora were found. In several instances sections of the lungs were stained by Gram's method, and aggregations of gram-positive cocci, probably staphylococci, were discovered in the bronchiolar exudate. The bacteriologic studies of postinfectious bronchiolitis, as described by other investigators, have been equally unsatisfactory. The number of our cases is too small for a study of seasonal influences. It is perhaps significant that none of our patients were Negroes although 30 per cent of the children in the Babies and Childrens Hospital during the years 1927 to 1932 were colored. We ascribe considerable importance to the fact that all our patients were infants and that in most of the cases the onset occurred in the first six months of life. Our opinion concerning the etiology of the disease is therefore confined to the fact that it occurs in young infants and is probably caused by an infection by common inhabitants of the upper respiratory tract.

SUMMARY

Subacute recurrent peribronchiolar pneumonia is a pulmonary disease of infants which has a characteristic composite of signs and symptoms. The history of repeated or continuous respiratory disease, the typical cough and the widespread obstruction of the smaller bronchioles make this diagnosis possible during the life of the patient. In eight of fourteen cases autopsies were obtained and substantiated the clinical diagnoses. Exudative and proliferative changes were found in and around the smaller respiratory passages, whereas the alveoli were relatively free from inflammation.

Little can be said concerning the etiology of the disease. It is probably a respiratory infection caused by common micro-organisms, which localizes at a site that has mechanical disadvantages for an infant otherwise possessing considerable resistance.

CARBOHYDRATE METABOLISM

II. RÔLE OF THE THYROID GLAND

J. A. JOHNSTON, M.D.
DETROIT

REVIEW OF THE LITERATURE

Evidences of an abnormal carbohydrate metabolism, hyperglycemia, glycosuria and diminished tolerance, as judged by the dextrose tolerance curve, have been described in hyperthyroidism.[1] The point has been at issue whether these findings could be explained as incidents of the accelerated metabolism or whether an intimate relationship between the pancreas and the thyroid, with the latter in the rôle of an antagonist, would not have to be invoked to explain the findings. John [2] reviewed the conflicting literature in 1927, and stated: "A number of authors, with whom I agree, believe that hyperthyroidism plays a fundamental etiologic rôle in the disturbance of endocrine equilibrium which constitutes the diabetic syndrome." It is known [3] that after the ingestion of thyroid substance the liver no longer retains glycogen as it previously did (increased glycogenolysis?). Du Bois [4] assumed that this explains the fact that although his patients with hyperthyroidism showed respiratory quotients of 0.94 and 0.98 after the ingestion of dextrose they did show glycosuria. Sanger and Hun,[1c] attempting to reconcile their elevated respiratory quotients and abnormal tolerance curves in hyper-

From the Departments of Pediatrics and Laboratories, Henry Ford Hospital.

1. (*a*) Geyelin, H. R.: The Carbohydrate Metabolism in Hyperthyroidism as Determined by Examination of Blood and Urine, Arch. Int. Med. **16**:975 (Dec.) 1915. (*b*) Wilder, R. M., and Sansum, W. D.: Glucose Tolerance in Health and Disease, ibid. **19**:311 (Feb.) 1917. (*c*) Sanger, B. J., and Hun, E. G.: Glucose Mobilization Rate in Hyperthyroidism, ibid. **30**:397 (Sept.) 1922. (*d*) Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, ibid. **38**:736 (Dec.) 1926.

2. John, H. J.: Hyperthyroidism Showing Carbohydrate Metabolism Disturbances: Ten Years Study and Follow Up of Cases, J. A. M. A. **99**:620 (Aug. 20) 1932.

3. Cramer, W., and Krause, R. A.: Carbohydrate Metabolism in Its Relation to the Thyroid Gland: The Effect of Thyroid Feeding on the Glycogen Content of the Liver and on the Nitrogen Distribution in the Urine, Proc. Roy. Soc., London, s. B **86**:550, 1913. Parhon, Marie: Sur la teneur en glycogen du foie et des muscles chez les animaux traites par des préparations thyroidiennes, J. de physiol. et de path. gén. **15**:75, 1913.

4. Du Bois, E. F.: Clinical Calorimetry: Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**:915 (June) 1916.

thyroidism, gave somewhat the same explanation, assuming a toxic effect of the pathologic thyroid gland on the hepatic cells. Shpiner [5] concluded, in 1927, that the hyperglycemia and glycosuria following medication with thyroid extract were simply due to the increased metabolic rate, since the injection of sodium nucleinate which produces an increased metabolic rate with fever results in a similar state of hyperglycemia. But in 1930,[6] working with partially depancreatized animals and finding that this thyroid effect became permanent and was always greater than that produced by the sodium nucleinate, he concluded that the influence of thyroid is not solely through its effect on basal metabolism, but possibly through some toxic effect of thyroxine on islet tissues of the pancreas. In this sense one might speak of an antagonism between pancreas and thyroid.

Wilder [1b] (1926) stated: "The phenomena exhibited by patients with diabetes combined with states of hyperthyroidism or hypothyroidism may be related to the general metabolic rate and thus may be explained without recourse to speculation as to a specific interdependence of thyroid and pancreas." Ernst and Kaufmann [7] attributed the greater susceptibility to insulin in the case of hyperthyroidism to the lowered glycogen content of the liver. That this may largely explain the "diminished tolerance" when it exists in hyperthyroidism is further strongly suggested by my studies on "starvation diabetes." [8] It was shown that the depletion of the stores of carbohydrate in the body resulted in a diminished oxidation of sugar administered until the depleted state had been remedied, and that a definite relationship could be shown to be maintained between the amount of carbohydrate being oxidized in a basal metabolic mixture and the amount that would be oxidized in a given time following the intravenous injection of dextrose. If carbohydrate in the basal mixture was accepted as reflecting the level of glycogen, and the known facts on starvation warranted this, the implication was that under usual circumstances glycogen was an obligatory metabolite of dextrose. The intimate relationship between protein and carbohy-

5. Shpiner, L. B.: Further Studies on Alleged Interrelationship of Pancreas and Thyroid, Am. J. Physiol. **83**:134 (Dec.) 1927.

6. Shpiner, L. B.: Increased Metabolism Only One Factor in Production and Maintenance of Hyperglycemia and Glycosuria in Experimental Hyperthyroidism, Am. J. Physiol. **92**:672 (April) 1930.

7. Ernst, Z., and Kaufmann, K.: Wechselbeziehungen zwischen Schilddrüse und Bauchspeicheldrüse, Ztschr. f. d. ges. exper. Med. **80**:694, 1932.

8. Johnston, J. A.: Carbohydrate Metabolism: I. Effect of Previous Diet on Utilization of Glucose Injected Intravenously, Am. J. Dis. Child. **46**:309 (Aug.) 1933.

drate was stressed, the correlation not holding unless the carbohydrate derived from protein was included in the calculation.

On the hypothyroid side the literature with reference to protein was reviewed by Janney,[9] from whose work the following two pertinent statements are taken: "The identical amount of thyroid which caused nitrogen loss with or without toxicity in normal individuals led to a large gain in nitrogen in the case of the cretin. . . . For the statement that 'cretins show a tendency to retain nitrogen easily' we find no experimental proof in an exhaustive study of the pertinent literature." Janney's own studies show definitely that the administration of therapeutic doses of thyroid to the cretin is followed by a marked increase in the retention of nitrogen. A detailed study of two cases of myxedema was reported by Boothby and his associates,[10] whose conclusions are essentially as follows: An immediate large increase in the elimination of total nitrogen following the administration of thyroid was followed by a gradual decrease while the metabolic rate was being elevated. At the end of from two to four weeks the value was the same as before the administration of thyroid, and equilibrium was again established on the same protein intake as before, but on a lower plane of deposit of protein and a higher level of production of heat. The following data are quoted from their second case (C. A.):

Date	Average Calories per Hour	Average Protein Intake, Mg. per 100 Cc.	Average Nitrogen Output, Mg. per 100 Cc.	Nitrogen Balance
7/24/28*	51	47.5	10	−3.4
9/ 8/12	59	59	5.68	+3

* One injection of 7 mg. of thyroxin, U. S. P., was given on July 24 and 31, and daily doses by mouth of 1.6 mg. after August 24.

The suggestion has been made that the effect of the administration of thyroid extract might be different in the period of growth from that observed in adults. The results reported by Weymuller, Wyatt and Levine[11] seem adequate to establish that the stimulation of the

9. Janney, N. W.: Studies in Thyroid Therapy, Arch. Int. Med. **22**:187 (Aug.) 1918.

10. Boothby, W. M.; Sandiford, Irene, and others: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects: I. A Method of Studying the Reserve or Deposit Protein, with a Preliminary Report of the Results Obtained, Ergebn. d. Physiol. **24**:728, 1925. Topper, A., and Cohen, P.: Effect of Thyroid Therapy on Children, Am. J. Dis. Child. **35**:205 (Feb.) 1928.

11. Weymuller, L. E.: Wyatt, T. C., and Levine, S. Z.: Respiratory Metabolism in Infancy and Childhood: Effect of Thyroid Therapy on Metabolism of Protein in Normal Infants, Am. J. Dis. Child. **43**:1544 (June) 1932.

energy metabolism in the normal infant by thyroid therapy is not necessarily at the expense of an excessive combustion of protein. Two of their cases showed what we have also found, that there is practically no increase in nitrogen paralleling a marked rise in calories, the rise being at the expense of fat and carbohydrate.

Janney and Isaacson [12] reported confirmation of the findings of hypoglycemia and increased tolerance for carbohydrate in hypothyroidism. In the protocol of the cretin studied by Du Bois,[4] it is pertinent to note that the percentage of calories derived from carbohydrate two and a half hours after the ingestion of a dextrose meal is less than in the hour following, i. e., three and a half hours after the ingestion of dextrose; the curve of oxidation shows an inversion.

Further, with reference to the inseparability of a consideration of protein and carbohydrate metabolism, Cramer [13] stated: "The specific protein-sparing action of carbohydrates in the general metabolism is due to carbohydrate protecting protein from being used by the liver for the formation of glycogen. The glycogen function . . . is stimulated by the sympathetic system and by the thyroid and adrenal hormones."

PLAN OF STUDY AND METHODS

There are reported here observations on four children over rather prolonged periods, two with hyperthyroidism, one cretin and one normal child to whom thyroid extract was administered. The details of the technic employed and the methods used are given elsewhere.[8] Briefly, determinations of metabolism were made under basal conditions, 40 cc. of a 50 per cent solution of dextrose was then injected intravenously, and determination were repeated at sixty, one hundred and twenty and one hundred and eighty minutes thereafter. With the urinary nitrogen and the respiratory quotient the metabolic mixture was calculated from the data of Lusk.[14] The dextrose oxidation curves were plotted as follows: The first point, *B*, is the number of grams of carbohydrate being oxidized in the basal hour calculated from the nonprotein respiratory quotient. The second, third and fourth points in the curve represent the amounts being oxidized one, two and three hours following the intravenous administration of 20 Gm. of dextrose given immediately after the basal run. As a comparison with what might normally be expected with this type of experiment, I brought out the fact that, for subjects of a given size, the dose of dextrose being constant, a fairly fixed ratio between the amount of carbohydrate being oxidized in the basal

12. Janney, N. W., and Isaacson, V.: I.: Blood Sugar in Endocrine Diseases, Arch. Int. Med. **22**:160 (Aug.) 1918.

13. Cramer, W.: Glycogenic Function of Liver and Its Endocrine Control, Brit. J. Exper. Path. **5**:128 (June) 1924.

14. Lusk, G.: Animal Calorimetry; Analysis of Oxidation of Mixtures of Carbohydrate and Fat, J. Biol. Chem. **59**:41 (Feb.) 1924.

metabolic mixture and the amount of carbohydrate oxidized in four hours with the injection of dextrose held. In the group studied, subjects of about the same age as those reported on in this communication, the ratio was approximately 1:3. This, of course, does not hold in complete starvation in which there may be an obliteration of oxidation of the administered dextrose, though there is still carbohydrate available from the protein in the basal mixture. In other words, the curve flattens as starvation is approached.

While for the most part the urinary nitrogen was determined only in the morning and early afternoon of the day on which the determinations of metabolic rate were made, as a check on this the total nitrogen value was determined for a period of two weeks on the cretin (case 4) and the normal child (case 3) and found to approximate closely enough to the figure obtained in the shorter period for the purposes of this study. Diets were calculated from standard food tables and weighed. In the experiment on the cretin the food was measured throughout only the last few months of the experiment; throughout the first part, it was only approximate, although the supper on the evening preceding the morning when each set of metabolic determinations was made was always the same and was accurately weighed. Dietary details of the other experiments appear in the protocols.

While particular interest centered on the metabolism of carbohydrate, the inseparability of this from the protein makes it impossible to ignore the latter, and in the case of the cretin its consideration constitutes the chief point of interest.

REPORT OF CASES

Hyperthyroidism.—CASE 1.—E. D. was operated on for hyperthyroidism in 1926, at the age of 6 years. (This case was reported in detail elsewhere[15] because of interest attached to the surgical aspects and the rarity of the condition at that age.) Six years following the operation there was a marked recurrence of the tumor on one side of the neck with the classic signs of toxic goiter: tremor, tachycardia, exophthalmos and lid lag. A section of the gland removed at operation on the second occasion showed hypertrophy and hyperplasia with colloid involution. The findings are summarized in chart 1 and table 1.

A study of the oxidation of dextrose on admission showed almost a flat curve, there being no carbohydrate oxidized in the second and third hours after the administration of 20 Gm. of dextrose, and only 0.73 Gm. in the first hour. Sixty-seven hundredths gram appeared in the urine. The dextrose-phosphorus curves (chart 2) were normal. After twelve days in bed on a diet high in calories the oxidation curve was again studied. At this time it was slightly higher than normal, there being 11.11 Gm. oxidized in the first hour, 4.88 Gm. in the second and 3.96 Gm. in the third. One and fifty-one hundredths gram of sugar was excreted (table 1). The total rate during this period had dropped from 77 to 63 calories an hour (+34 to +10). The conclusion from this set of observations was that there was no impairment of oxidation in hyperthy-

15. McGraw, A. B.: Juvenile Exophthalmic Goiter, Surg., Gynec. & Obst. **47**:25 (July) 1928.

roidism in the presence of adequate stores of glycogen; rather there would seem to have been an acceleration of this in common with other metabolic processes.

CASE 2.—C. R. presented at the age of 12 years a typical picture of exophthalmic goiter: sweating of the palms, tremor, tachycardia, exophthalmos and swelling of the gland. At operation there was found third degree hyperplasia with colloid involution and areas of necrosis and infarction. The findings are summarized in chart 3 and table 2.

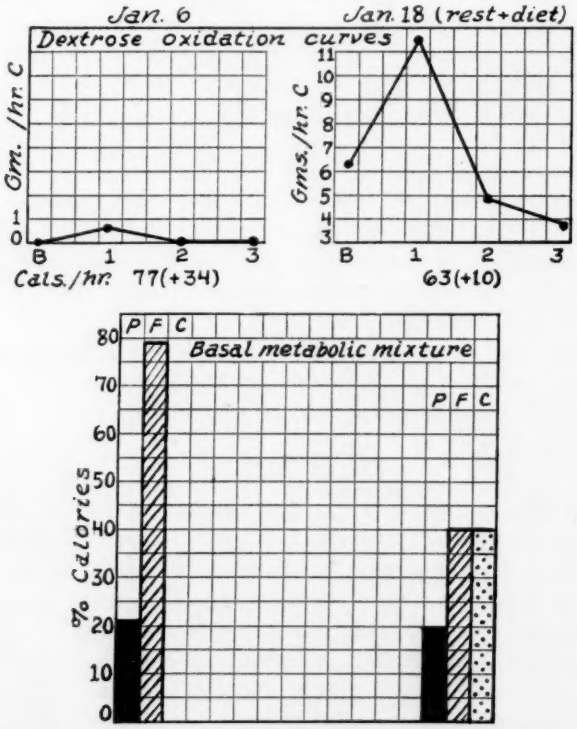

Chart 1 (case 1).—Dextrose oxidation curves. The first curve on January 6 shows an almost complete abolition of the oxidation of sugar; the second curve on January 18, after a diet high in calories and a period of rest in bed shows an oxidative response greater than normal. The basal metabolic mixture on the morning the second set of observations were made showed that 40 per cent of the calories were derived from carbohydrate. The curves are interpreted as showing that the apparent inhibition of oxidation does not occur in the presence of adequate glycogen stores as far as these are reflected in the amount of carbohydrate available in the basal metabolic mixture. In this and subsequent charts the dextrose oxidation curves were plotted as follows: the first point, *B*, is the number of grams of carbohydrate being oxidized in the basal hour calculated from the nonprotein respiratory quotient; points 1, 2 and 3 in the curve represent the amounts being oxidized one, two and three hours following the intravenous administration of 20 Gm. of dextrose given immediately after the basal run. The solid black area, *P*, indicates protein; the cross-lined area, *F*, fat, and the stippled area, *C*, carbohydrates.

TABLE 1.—*Total Metabolism and Percentage Composition of the Metabolic Mixture in Case 1 Under Basal Conditions and Following Intravenous Injection of Dextrose Before and After Rest and High Caloric Feeding*

Date	Weight, Pounds		Metabolism: Calories per Hour	Protein: Gm.	Protein: Per Cent Calories	Fat: Gm.	Fat: Per Cent Calories	Carbohydrate: Gm.	Carbohydrate: Per Cent Calories	Basal Metabolic Rate	Non-protein Respiratory Quotient	Comment
1/ 6/32	79	B*	77.8	4.1	22.0	6.5	78.0	0	0	+34	0.67	Diet, 2,406 calories: protein, 10 per cent (60 Gm.); fat, 39 per cent; carbohydrate, 51 per cent
		1	78.1			6.2		0.73			0.72	
		2	72.2			5.9		0			0.67	
		3	71.2			5.8		0			0.70	
1/18/32	77¼	B	63.12	3.14	20.4	2.72	40.1	6.09	39.5	+10	0.85	Diet, 2,975 calories: protein, 15 per cent (110 Gm.); fat, 35 per cent; carbohydrate, 50 per cent; started 1/16
		1	61.52		21.0	0.33	5.0	11.11	74.0		0.98	
		2	60.09		21.4	2.92	45.3	4.88	33.3		0.83	
		3	65.43		19.6	3.91	55.5	3.96	24.8		0.79	

* B refers to the calculations for the basal hour; 1, 2 and 3 to the first, second and third hours following the injection of 20 Gm. of dextrose intravenously.

The curves of oxidation show a steady rise following each operative procedure, paralleling a rise in the carbohydrate available in the basal mixture. The last two curves, made while the metabolic rate was still considerably above normal, are abnormally high.

It is worth noting that relatively the percentage of calories derived from protein in the last three experiments is low, while the rate is still high, but the reserve of glycogen has presumably been restored, as judged by the composition of the basal metabolic mixture.

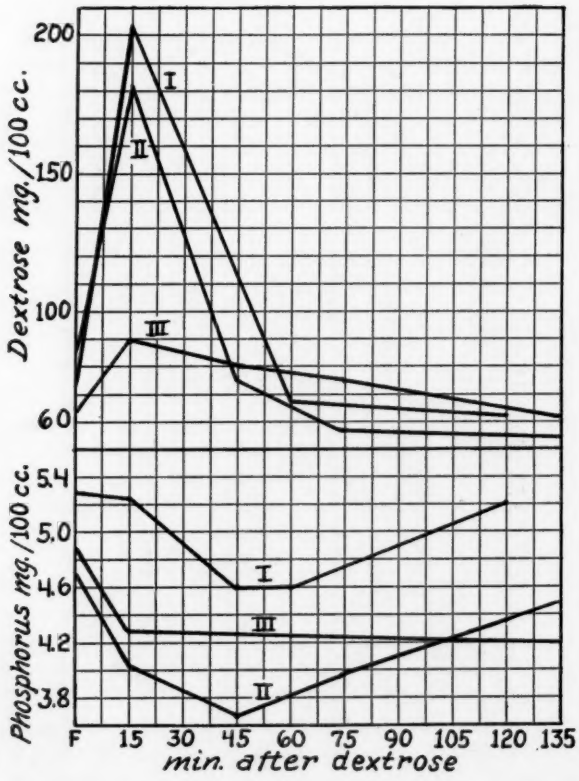

Chart 2.—Dextrose-phosphorus curves with 50 cc. of 50 per cent dextrose injected intravenously. Curve *I* for case 3 and curve *II* for cases 1 and 2 are normal. Curve *III*, for case 4, shows an "increased tolerance" and a failure of the phosphorus to recover. *F* means the percentage of calories from fat.

Obesity with a Normal Rate.—CASE 3.—This patient's physical examination revealed no abnormality except obesity. The dextrose-phosphorus curve and roentgenograms of the sella turcica and of the epiphyses gave no evidence of glandular disturbance. The metabolic rate on the basis of surface area was between —3 and —6 on four occasions. The observations are recorded in table 3 and chart 4.

A marked increase in the total number of calories was not accompanied by diminution in the oxidation of dextrose other than that related to a lowered basal carbohydrate level; in fact, more injected dextrose was oxidized during the last two experiments than during the first two. It is interesting that a positive nitrogen balance was maintained on a relatively small intake with a markedly increasing metabolic rate.

Cretinism.—CASE 4.—This patient was not treated for twelve years, her age when first seen. At this time she was a heavy-set, dull appearing child. Her

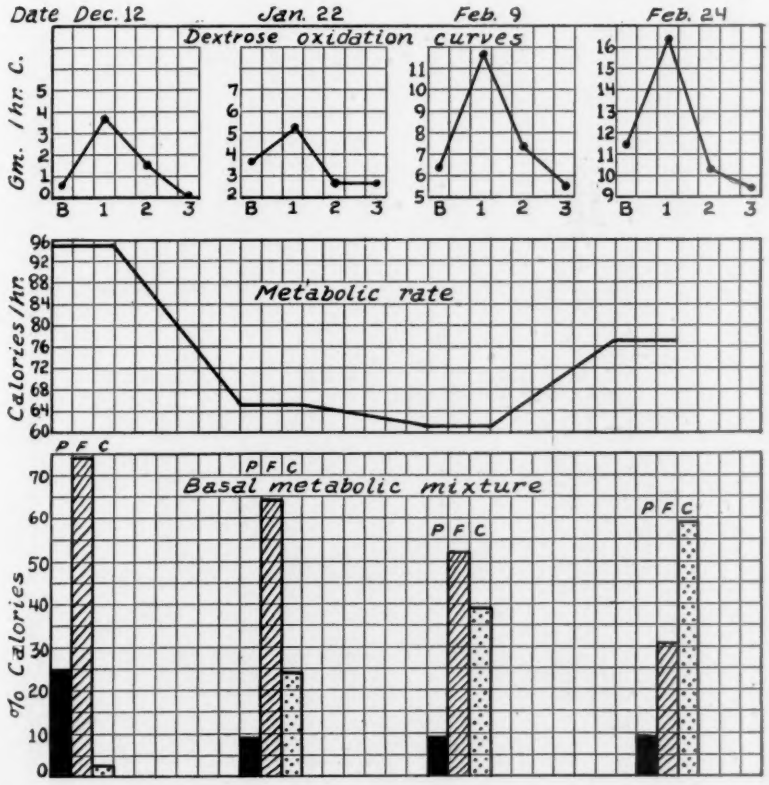

Chart 3 (case 3).—Between the first and second observations a ligation and lobectomy on the right were done; between the second and third, a partial lobectomy on the left. A progressive increase in the amount of dextrose oxidized occurs following each surgical procedure and paralleling successive increases in the amount of carbohydrate in the basal metabolic mixture. Note that during the fourth observation the metabolic rate has again risen, but the increase in oxidation continues and is greater than normal.

height was 49¾ inches (126.37 cm.); her weight, 79 pounds (35.8 Kg.). The skin was dry, with a slatelike feel; the hair coarse, but not dry; the voice a deep bass and harsh; the tongue thick; the teeth showing marked caries; the thyroid gland not palpably enlarged; the breasts pendulous; the nipples large and inverted; the heart normal (blood pressure 102 systolic and 78 diastolic); the abdomen lax

TABLE 2.—*Total Metabolism and Percentage Composition of the Metabolic Mixture in Case 2 Under Basal Conditions and Following Intravenous Injection of Dextrose Before and After Various Indicated Operative Procedures*

Date	Weight, Pounds		Metabolism: Calories per Hour	Protein: Gm.	Protein: Per Cent Calories	Fat: Gm.	Fat: Per Cent Calories	Carbohydrate: Gm.	Carbohydrate: Per Cent Calories	Basal Metabolic Rate	Comment
12/16/30	93.5	B*	95.48	4.26	18	7.92	78	0.90	4	+73	
		1	95.65	4.26	18	6.75	66	3.56	16		
		2	88.40	4.26	20	6.93	73	1.44	6		
		3	87.90	4.26	20	7.51	80	0.00	0		
12/31/30											Ligation
1/ 9/31											Right lobectomy
1/22/31	80	B	64.98	1.4	9	4.69	67	3.80	24	+23	
		1	71.80	1.4	8	4.70	61	5.37	31		
		2	71.23	1.4	8	5.87	78	2.46	14		
		3	72.42	1.4	8	6.00	72	2.53	4		
1/26/31											Left lobectomy
2/ 9/31	85.5	B	62.0	1.65	10	3.58	51	6.27	39	+24	
		1	66.0	1.65	10	1.50	20	11.86	70		
		2	65.8	1.65	10	3.55	48	7.04	42		
		3	62.7	1.65	11	4.03	56	5.35	33		
2/24/31	92.5	B	77.25	1.8	9	2.7	32	11.45	59	+37	
		1	75.57	1.8	10	0.0		16.51	90		
		2	73.52	1.8	10	2.5	32	10.35	58		
		3	73.35	1.8	10	2.8	36	9.78	54		

* B refers to the calculations for the basal hour; 1, 2 and 3 to the first, second and third hours following the injection of 20 Gm. of dextrose intravenously.

TABLE 3.—*The Oxidation of Dextrose Administered Intravenously in Case 3 During the Administration of Thyroid Extract*

Date	Weight, Pounds		Metabolism: Calories per Hour	Protein: Gm.	Protein: Per Cent Calories	Fat: Gm.	Fat: Per Cent Calories	Carbohydrate: Gm.	Carbohydrate: Per Cent Calories	Basal Metabolic Rate	Comment
11/19	171	B*	65.90	3.88	24.0	3.77	54.0	3.65	22.0	— 4	Diet, 2,000 calories: protein 17 per cent (83 Gm.); fat, 37 per cent; carbohydrate, 46 per cent
		1	66.75			3.2		5.08			
		2	65.07			3.38		4.33			
		3	64.79			4.3		2.07			
3/ 7	153	B	61.96	2.92	19.3	3.73	55.9	3.74	24.8	— 9	
		1	61.96			3.08	46.2	5.21	34.5		
		2	59.05			2.25	35.5	6.37	44.3		
		3	63.78			4.18	60.9	3.16	20.3		
4/15	142	B	74.82	3.91	21.5	6.08	75.5	0.55	3	+14	
		1	75.08			5.37		2.25			
		2	74.32			4.95		2.99			
		3	78.06			6.28		3.59	0.87		
4/25	139	B	82.38	3.38	16.8	6.96	78.6	0.91	4.5	+26	
		1	91.54			5.95	60.4	5.43	24.3	+40	
		2	91.72			7.17	72.7	2.72	12.1		
		3	92.85		14.9	8.00	80.1	1.12	4.9		

* B refers to the calculations for the basal hour; 1, 2 and 3 to the first, second and third hours following the injection of 20 Gm. of dextrose intravenously.

and protuberant, and the extremities relatively short. A roentgenogram of the skull showed a normal appearing sella turcica, and the ephiphyses were normal. The intelligence quotient was 38.

Two points of particular interest appear in the data in chart 5 and table 5. An unusually high percentage of the calories was derived from protein and there was, just as in the case reported by Janney, a relative and absolute diminution in the oxidation of this foodstuff as the metabolic rate rose following the administration of thyroid extract and an increase as the metabolic rate fell with the

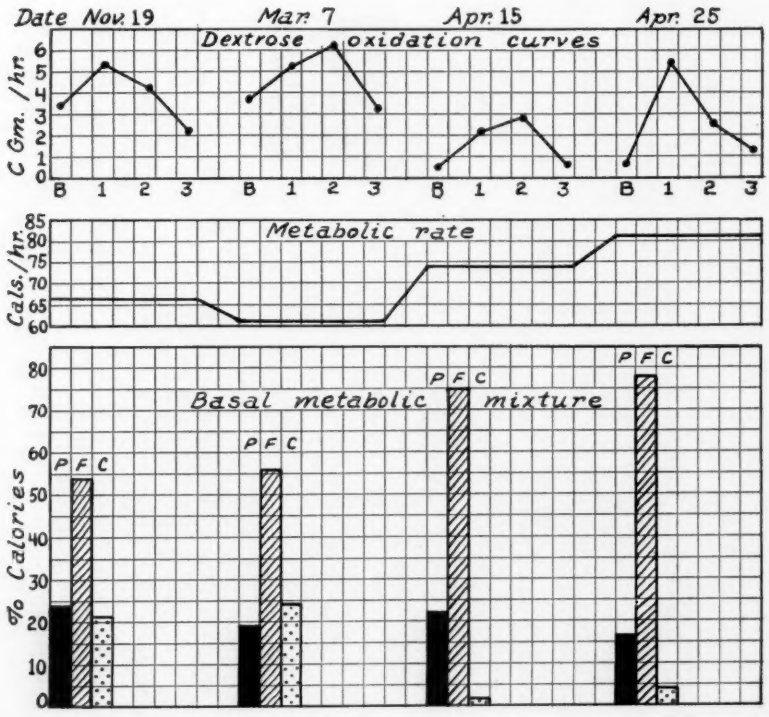

Chart 4 (case 3).—The oxidation of dextrose is normal as related to the amount of carbohydrate in the basal metabolic mixture.

TABLE 4.—*Urinary Nitrogen at Several Levels of Metabolism in Case 3*

Date	24 Hours			
	Food, Calories	Food Nitrogen, Mg.	Urine Nitrogen, Mg. per 100 Cc.	Basal Calories per Hour
	2,000	13.3		
3/ 6	.....	....	8.6	1,487
3/ 7	.....	....	10.7	
3/ 8	.....	....	8.83	1,786
4/13	.....	....	7.0	
4/14	.....	....	12.8	
4/15	.....	....	11.9	
4/19	.....	....	11.2	
4/20	.....	....	9.5	
4/21	.....	....	10.4	
4/22	.....	....	10.5	
4/24	.....	....	11.9	
4/25	.....	....	12.8	1,977

discontinuance of thyroid therapy. The increase in the total number of calories was at the expense of fat. Equally interesting is the behavior of the dextrose oxidation curve. This is inverted until after the peak of the effect of medication with thyroid extract, as judged by the total rate, has been reached. Some effect is evident on the total rate and the protein metabolism for as long as seven weeks following the discontinuance of therapy.

The inversion of the curve may be in intimate relationship to the edema of the cretin; the resumption of the normally erect type of curve coincides with the time when the water of the tissues has been released.

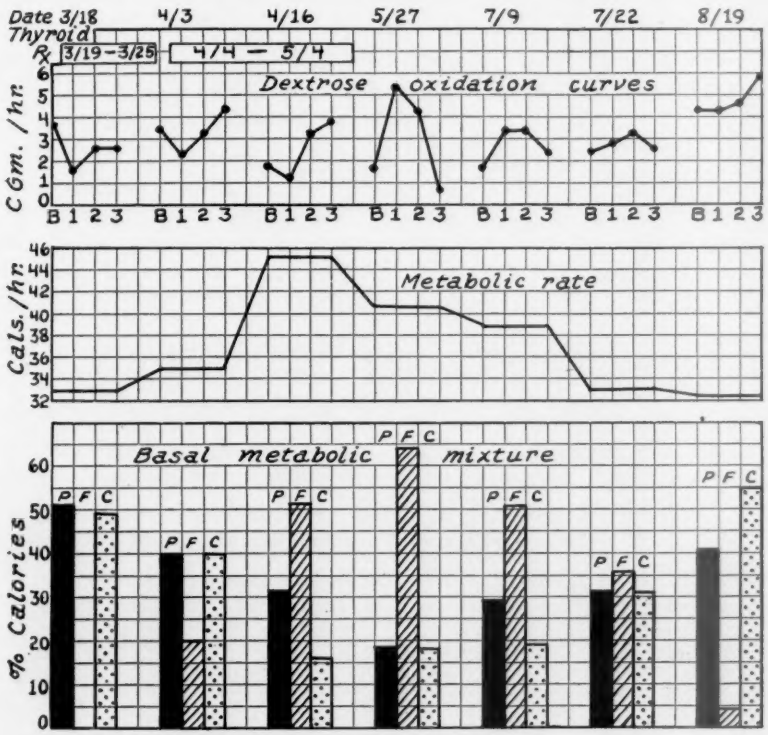

Chart 5 (case 4).—The first normal erect type of curve is noted on May 27. There is a progressive decrease, both relative and absolute, in the protein oxidized with a steady increase in fat under the influence of thyroid extract. The effect persists in part for more than seven weeks afer the discontinuance of thyroid therapy.

An identical set of curves (inverted before and erect after the administration of thyroid extract) was observed in a case of nephrosis in which also profound diuresis followed the administration of thyroid extract. This phase of the subject will be discussed in a subsequent communication dealing with the relation of salt and water to the utilization of sugar.

TABLE 5.—*Total Metabolism and Percentage Composition of the Metabolic Mixture in Case 4*

Date	Weight, Pounds		Metabolism: Calories per Hour	Protein: Gm.	Protein: Per Cent Calories	Fat: Gm.	Fat: Per Cent Calories	Carbohydrate: Gm.	Carbohydrate: Per Cent Calories	Basal Metabolic Rate	Comment
3/18/31	81	B*	32.8	3.96	50.3	0	0	3.9	49.7	—35	Diet, approximately 2,000 calories: protein, 13 per cent (67 Gm.); fat, 51 per cent, and carbohydrate, 36 per cent; supper night before test weighed: protein, 22 Gm.; fat, 38 Gm.; carbohydrate, 38 Gm.
		1	33.3			1.10		1.64			
		2	34.1			0.82		2.51			
		3	33.4			0.78		2.40			
3/19 to 3/25											Dried thyroid extract, 3 grains (0.195 Gm.) a day
4/ 3/31	91	B	35.9	3.48	40	0.74	19.5	3.50	40.5	—32	
		1	36.4			1.42		2.18			
		2	34.8			0.72		3.37			
		3	36.6			1.01		4.10			
4/4 to 5/4											Dried thyroid extract, 6 grains (0.39 Gm.) a day
4/16	88½ (52)	B	45.7	3.50	32	2.57	52	1.72	16	—12	
		1	46.2			3.06		1.28			
		2	44.9			2.08		3.19			
		3	48.5			2.77		3.67			
5/ 4											Thyroid therapy discontinued
5/27	91¼	B	40.8	1.73	18	2.78	64	1.86	18	—23	
		1	42.5			1.75		5.37			
		2	41.0			2.14		4.23			
		3	45.3			3.91		0.81			
6/ 4											Diet from this point accurately weighed: calories, 1,485; protein 13 per cent (48 Gm.); fat, 46 per cent carbohydrate, 41 per cent
	95	B	36.1	2.62	29	1.98	52.5	1.60	18.5	—32	
		1	35.2			1.35		3.71			
		2	35.0			1.08		3.81			
		3	35.1			0.90		5.85			
7/22	95	B	34.0	2.56	32	1.31	36	2.66	32	—35	
		1	35.5			1.46		2.96			
		2	33.0			1.14		3.04			
		3	33.4			1.83		2.80			
8/19	96	B	33.2	3.30	41	0.13	4	4.39	55	—37	
		1	34.0			1.09		4.33	52		
		2	34.3			0.89		4.91	59		
		3	34.5			0.76		5.92	69		

* B refers to the calculations for the basal hour; 1, 2 and 3 to the first, second and third hours following the injection of 20 Gm. of dextrose intravenously.

COMMENT

With the acceleration of the metabolism rate generally, there is an increase in the oxidation of dextrose until the glycogen stores are depleted; there is then the same diminution that is always seen with depleted stores. Dann and Chambers [16] have shown that in fasting dogs dextrose thus failing of oxidation is accounted for as glycogen. This, to my mind, would oppose Cramer's idea that glycogenesis is inhibited. The alternative explanation, that glycogenolysis is accelerated, is consonant with all the known facts and is the interpretation suggested by Richardson and Levine.[17] The inverted curves seen in the cretin may be explained as a retarded release of glycogen, since oxidation is unimpaired. There is implicit in this explanation the concept of glycogen as an obligatory metabolite of dextrose.

Regarding the protein metabolism, the findings can be explained as due to a marked sparing of this metabolite with the increased oxidation of, first, carbohydrate so long as it is available, and, subsequently, fat, as the glycogen stores are depleted.

CONCLUSIONS

1. There is no impairment of oxidation of carbohydrate in hyperthyroidism. If the glycogen stores are maintained, injected carbohydrate is oxidized more readily in patients with hyperthyroidism than in normal persons.

2. The diminution in oxidation sometimes seen in hyperthyroidism is the phenomenon of "starvation diabetes," resulting secondarily from increased glycogenolysis and accelerated metabolism.

3. The increased oxidation of injected carbohydrate in hyperthyroidism is interpreted as due to improved glycogenolysis, and the delay in oxidation in the cretin despite adequate glycogen stores, as due to decreased glycogenolysis.

4. There is a marked sparing action on protein following medication with thyroid extract in the cretin, the result of an increased availability of glycogen stores and a heightened oxidation of fat.

5. A relationship exists between the release of water from the body and the mobilization of sugar.

Dr. F. W. Hartman supervised the determinations of the metabolic rate, Dr. O. H. Gaebler criticized the manuscript, and Dr. R. J. Mason assisted in the preparation of the subjects.

16. Dann, M., and Chambers, W. H.: Glycogenesis from Glucose Administered to Fasting Dog, J. Biol. Chem. **95**:413 (March) 1932.

17. Richardson, H. B.; Levine, S. Z., and Du Bois, E. F.: Clinical Calorimetry; Storage of Glycogen in Exophthalmic Goiter, J. Biol. Chem. **67**:737 (March) 1926.

BODY BUILD IN INFANTS

IV. THE INFLUENCE OF RETARDED GROWTH

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In a previous report [1] the body builds of two groups of healthy infants were compared. One group, studied at Bellevue Hospital, was derived from poverty-stricken homes and consisted of abandoned infants and infants left in the hospital because of illness of the mothers; the other group, cared for in a well baby clinic at the Fifth Avenue Hospital, consisted of infants from families with moderate incomes. The racial make-up of the groups was similar and was found to be without influence on the dimensions studied.

Measurements made on the two groups showed that the infants from the poverty-stricken homes were shorter and weighed less than did those from the more favorable environment. Moreover, the body builds of the two groups were found to differ, the lateral dimensions of the group at Bellevue Hospital, in relation to total body length, being significantly smaller than similar dimensions for the group from the clinic of the Fifth Avenue Hospital.

It was suggested that the differences in body build were dependent on differences in the rate of growth. It is well known that when growth during infancy is retarded weight is more strikingly influenced than total body length. Measurements of various lateral dimensions showed that these dimensions were also more strikingly affected than total body length. There resulted a change in body build in the direction of relative narrowness or "linearity" of the retarded infants.

Numerous observations in animals indicate that dietary restrictions result in a change in body form. The subject has been recently reviewed by Smith.[2] When animals (steers,[3] puppies [4] and rats [5]) are

From the Children's Medical Service of Bellevue Hospital and the Department of Pediatrics, New York University and the Fifth Avenue Hospital.

1. Bakwin, H., and Bakwin, R. M.: Body Build in Infants: II. The Proportions of the External Dimensions of the Healthy Infant During the First Year of Life, J. Clin. Investigation **10**:377, 1931.

2. Smith, A. H.: Phenomena of Retarded Growth, Editorial Rev. **4**:427, 1931.

3. Waters, H. J.: Proc. Soc. Prom. Agric. Sc. **29**:71, 1908; **30**:70, 1909; quoted by Smith.[2]

4. Aron, H.: Nutrition and Growth, Philippine J. Sc (Sec. B) **6**:1, 1911.

5. Jackson, C. M.: J. Exper. Zoöl. **19**:99, 1915. Quinn, E. J.; King, C. G., and Dimit, B. H.: A Study of the Effects of Certain Diets upon the Growth and Form of Albino Rats, J. Nutrition **2**:7, 1929.

maintained on diets which do not permit increase in weight, they continue to grow in length at a rate only slightly less than normal. Waters [3] found that the length of the foreleg and the head in steers also increased, as did the depth of the thorax.

The purpose of the present study was to determine the influence of improved care on the growth and body proportions of infants from the poverty-stricken district. With this aim in view, a third group was studied in a health clinic for infants born in Bellevue Hospital and residing in the vicinity of the hospital. A worker visited the obstetric wards, distributing appointment cards to mothers residing in the district and urging them to bring their infants to the clinic for advice. The obstetric service cooperated by further urging the mothers when they returned for obstetric follow-up. Post-cards and visits to the home were later used.

The infants (176 boys measured 495 times and 177 girls measured 555 times) were seen at monthly intervals or more frequently. Advice was given regarding general care, with particular emphasis on diet. In some instances families were aided with milk and occasionally with other foods. Cod liver oil was distributed free at the pharmacy. Habit-training was stressed, and records were kept of various aspects of development.

The infants in this group were from the same social environment as those admitted to the wards at Bellevue Hospital. It was not possible to obtain accurate estimates of the incomes of families because of the rapid changes in income of this section of the population as the economic depression progressed. In March 1933, when the data for this report were assembled, most of the families were being cared for partly or wholly by various relief agencies.

The measurements of the two groups previously described have been continued, and the groups enlarged. The group at the Fifth Avenue Hospital consisted of 267 males measured 710 times and 247 females measured 695 times. The unsupervised group at the Bellevue Hospital consisted of 373 males measured 455 times and 321 females measured 343 times and included infants with mild infection of the upper respiratory tract as well as healthy infants. All other illnesses were excluded. Measurements were usually made within a few days after admission to the hospital. Infants with mild infections of the upper respiratory tract were found to have body proportions similar to those of well infants, although continuous or repeated infections probably influence body build in infants through interference with nutrition.

Definitions of the terms used, descriptions of the technic of measurement and statistical analysis and a consideration of the sources of error

were discussed in a previous report.[6] All anthropometric measurements were made by Miss Allene Jones.

Thirty-three measurements (including weight) were made on each infant. In this report only the lateral dimensions (the bimalar and bigonial diameters of the face, the circumference of the thorax at the

Comparison of Heights and Weights of Three Groups of Infants by Certain Subdivisions of Age Under 1 Year

	Males					Females				
		Vertex		Weight			Vertex		Weight	
Age, Weeks	Number of Cases	Average, Mm.	Standard Deviation, Mm.	Average, Gm.	Standard Deviation, Gm.	Number of Cases	Average, Mm.	Standard Deviation, Mm.	Average, Gm.	Standard Deviation, Gm.
Fifth Avenue Hospital Clinic										
Birth	205	511.6	16.3	3,502	538	249	503.4	19.2	3,372	458
0- 3	183	519.8	23.3	3,515	570	172	510.5	19.5	3,380	424
4- 7	81	555.7	26.0	4,585	658	63	545.5	20.9	4,246	570
8-15	117	597.5	32.5	5,750	720	101	589.5	23.1	5,310	720
16-23	93	649.4	23.4	7,090	750	104	632.9	23.7	6,440	760
22-31	85	687.9	23.7	8,207	1,000	79	674.9	20.0	7,670	800
32-39	63	718.8	28.8	9,291	1,052	67	698.2	19.3	8,460	824
40-47	57	741.6	28.0	10,060	1,184	44	733.9	25.3	9,200	1,068
48-55	31	768.9	24.8	10,800	1,210	59	748.2	22.1	9,900	1,044
Bellevue Hospital Clinic										
Birth	470	504.0	20.5	3,443	490	416	498.1	19.2	3,339	463
0- 3	88	527.5	23.5	3,683	587	102	521.0	20.2	3,553	560
4- 7	78	551.8	25.8	4,275	789	52	542.1	19.4	4,035	574
8-15	93	600.0	27.6	5,408	752	57	587.2	27.5	5,340	832
16-23	75	646.2	24.5	6,883	920	28	626.0	22.8	6,920	692
24-31	54	684.2	18.3	7,980	824	29	666.0	20.9	7,516	982
32-39	42	710.5	31.2	8,920	1,000	33	691.5	25.4	8,296	1,236
40-47	31	728.2	31.1	9,440	1,040	18	717.0	22.9	8,800	928
48-55	22	761.3	22.7	10,420	896	24	740.6	27.6	9,368	1,200
Bellevue Hospital										
Birth	470	504.0	20.5	3,443	490	416	498.1	19.2	3,339	463
0- 3	101	513.1	24.3	3,310	500	96	509.2	23.5	3,210	514
4- 7	40	548.4	25.7	3,900	640	52	531.9	25.1	3,592	642
8-15	78	583.1	34.1	4,533	882	52	568.9	31.1	4,280	1,043
16-23	63	631.0	39.5	5,632	1,215	31	606.9	31.2	5,032	1,125
24-31	42	662.4	30.8	6,304	1,152	32	651.9	32.7	6,276	1,136
32-39	37	697.4	30.3	7,492	1,060	33	680.2	30.6	7,188	1,259
40-47	35	717.7	37.1	7,982	1,771	21	709.8	46.0	7,848	1,548
48-55	27	728.0	31.1	8,280	1,135	25	729.4	27.4	8,288	1,316

nipples and the biacromial and bicristal diameters of the trunk), height and weight are considered.

The weights and heights of the three groups of infants during the first year of life are compared in the table. The table also shows the

6. Bakwin, H., and Bakwin, R. M.: Body Build in Infants: I. The Technique of Measuring the External Dimensions of the Body in Infants, J. Clin. Investigation **10**:369, 1931.

number of infants at each age subdivision under 1 year. Infants born in Bellevue Hospital weigh slightly but significantly less at birth than infants born in the Fifth Avenue Hospital. There was little difference in the gain in weight for the supervised groups at Bellevue and the Fifth Avenue Hospitals, the boys weighing about 10,800 Gm. and the girls about 9,980 Gm. at the end of the first year. The unsupervised group

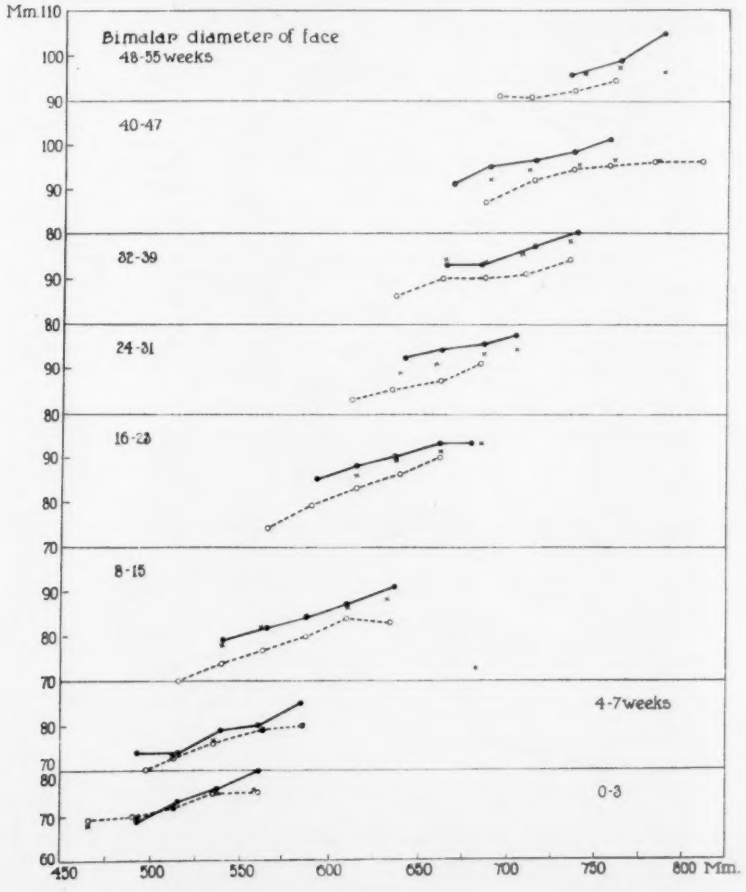

Chart 1.—The relation of the bimalar diameter of the face to the total body length by certain subdivisions of age under 1 year. Continuous lines connect the averages, represented by dots, for the supervised group at the Bellevue Hospital; dotted lines connect the averages, represented by circles, for the unsupervised group at the Bellevue Hospital, and crosses represent averages for the group at the Fifth Avenue Hospital.

of infants admitted to Bellevue Hospital, however, showed a marked delay, the boys and girls weighing about 8,200 Gm. at the end of the first year, a delay of from 1,800 to 2,600 Gm.

Infants born in Bellevue Hospital are slightly but significantly shorter than infants born in the Fifth Avenue Hospital. The gain in total body length was most rapid for the group at the Fifth Avenue Hospital clinic, the boys measuring 765 mm. and the girls 745 mm. at the end of the first year. The infants at the Bellevue Hospital well baby clinic were slightly shorter; the unsupervised Bellevue Hospital group were the shortest, the boys and girls measuring about 730 mm. at the end of the first year.

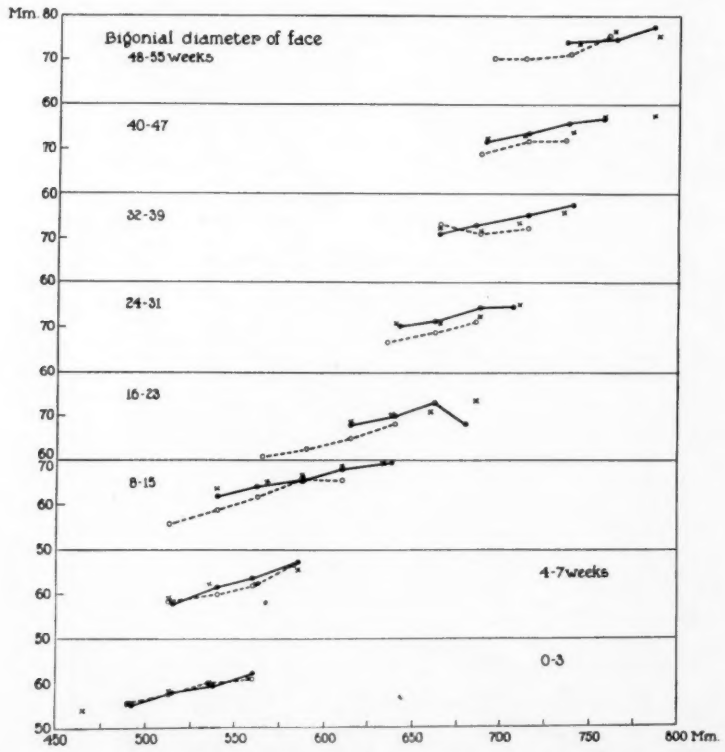

Chart 2.—The relation of the bigonial diameter of the face to the total body length by certain subdivisions of age under 1 year.

It is interesting to note that the delay in growth as measured by the weight and the height was more marked for boys than for girls, indicating a greater susceptibility on the part of male infants to adverse environment. The higher mortality of male infants has long been known.[7]

The relation of various lateral dimensions (the bimalar and bigonial diameters of the face, the circumference of the chest at the nipples, and the biacromial and bicristal diameters of the trunk) to total body length, by certain subdivisions of age under 1 year, is shown in charts 1,

7. Clarke, J.: Observations on Some Causes of the Excess of Mortality of Males Above that of Females, Phil. Tr. Roy. Soc. London **16**:122, 1786.

2, 3, 4 and 5. Data for both sexes were plotted together, since no difference was found when calculations were made separately in relation to body length.

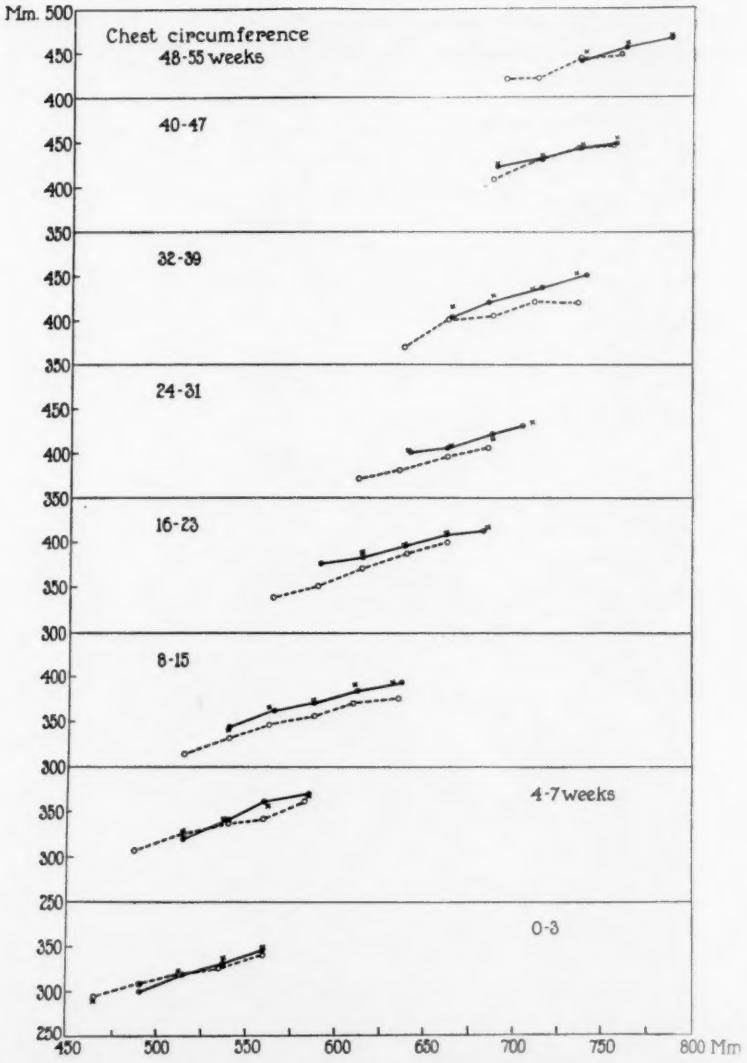

Chart 3.—The relation of the circumference of the chest at the nipples to the total body length by certain subdivisions of age under 1 year.

During the first four weeks of life, the body proportions of all groups were similar. During the second four weeks, the supervised groups tended to have relatively larger lateral dimensions than the unsupervised group. After the eighth week, the supervised groups

(the Bellevue Hospital clinic, represented by continuous lines, and the Fifth Avenue Hospital clinic, represented by crosses) showed regularly larger lateral dimensions in relation to total body length than did the hospital group (dotted lines).

In chart 6 the percentage growth rates of various dimensions for the three groups of infants are compared by twelve week periods during

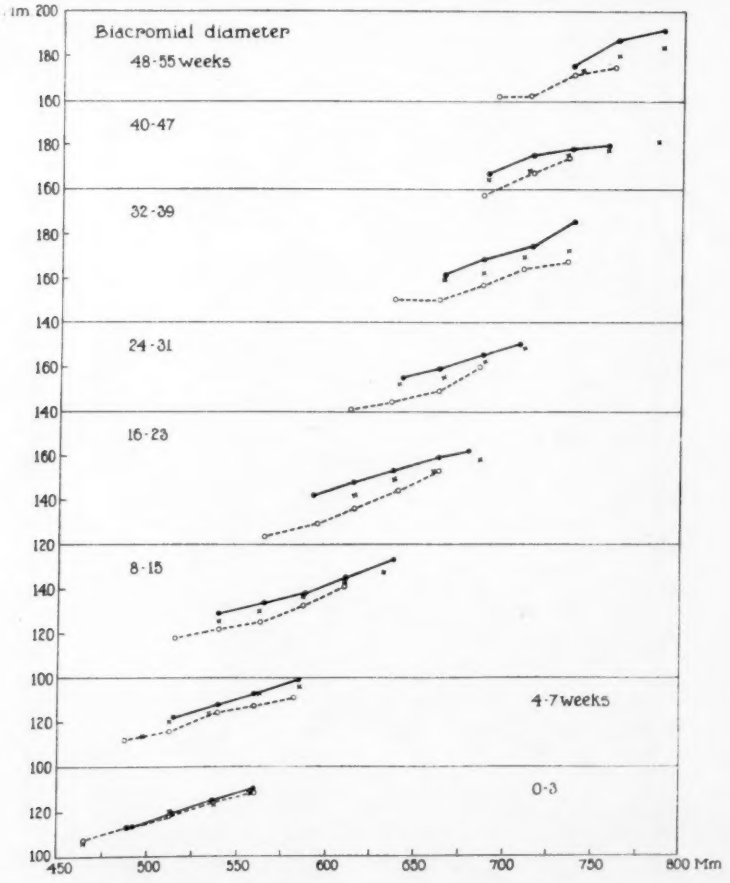

Chart. 4.—The relation of the biacromial diameter of the trunk to the total body length by certain subdivisions of age under 1 year.

the first forty-eight weeks of life. The percentage rates have been calculated according to the logarithmic formula suggested by Brody.[8]

8. Percentage growth $= 100 \times 2.3 \times \log_a - \log_b$, in which b is the size of the dimension at the beginning and a is the size of the dimension at the end of the period. (Brody, S.: Growth and Development: III. Growth Rates, Their Evaluation and Significance, University of Missouri, College of Agriculture Research Bulletin, no. 97, 1927).

The delay in growth of the retarded group has occurred entirely during the first twelve weeks of life. Thereafter the percentage growth for all three groups continues at approximately the same rate. The chart

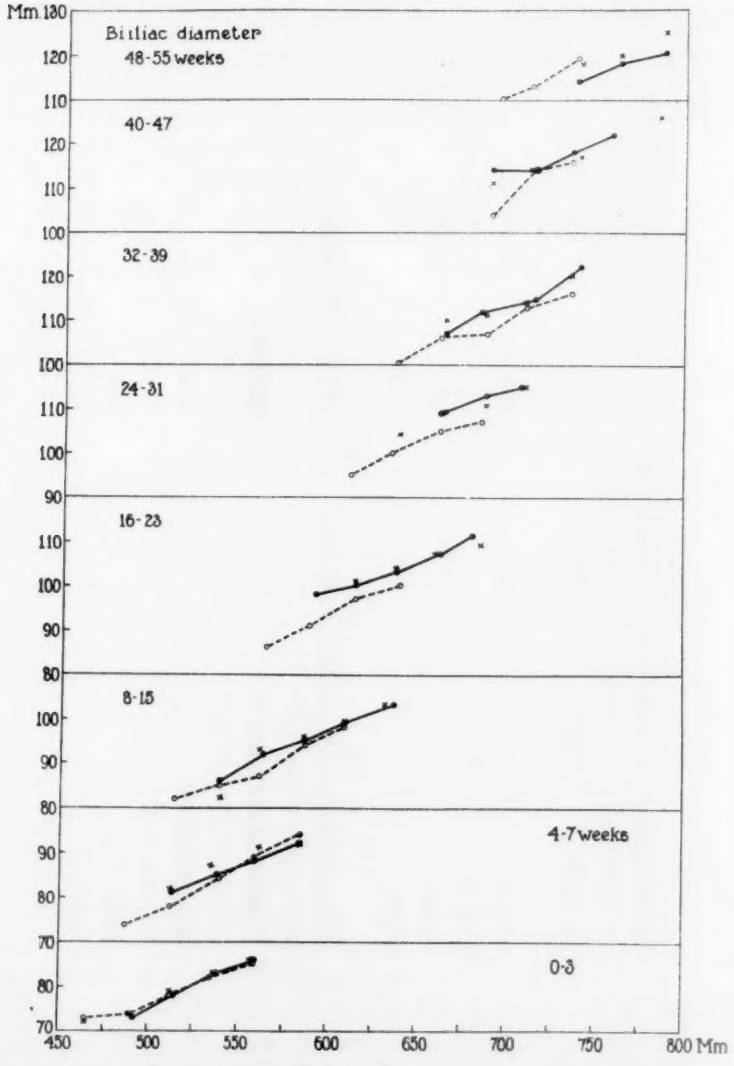

Chart 5.—The relation of the bi-iliac diameter of the trunk to the total body length by certain subdivisions of age under 1 year.

also illustrates what has already been suggested, namely, that the delay in growth of the total body length is less than the delay in growth of the lateral dimensions.

It might be suspected that there is a correlation between the rate of growth and the degree of retardation, the more rapidly growing dimensions being more markedly delayed than those growing more slowly, or vice versa. Comparison of the heights of the columns in chart 6, however, indicates that no such relationship exists. During the first

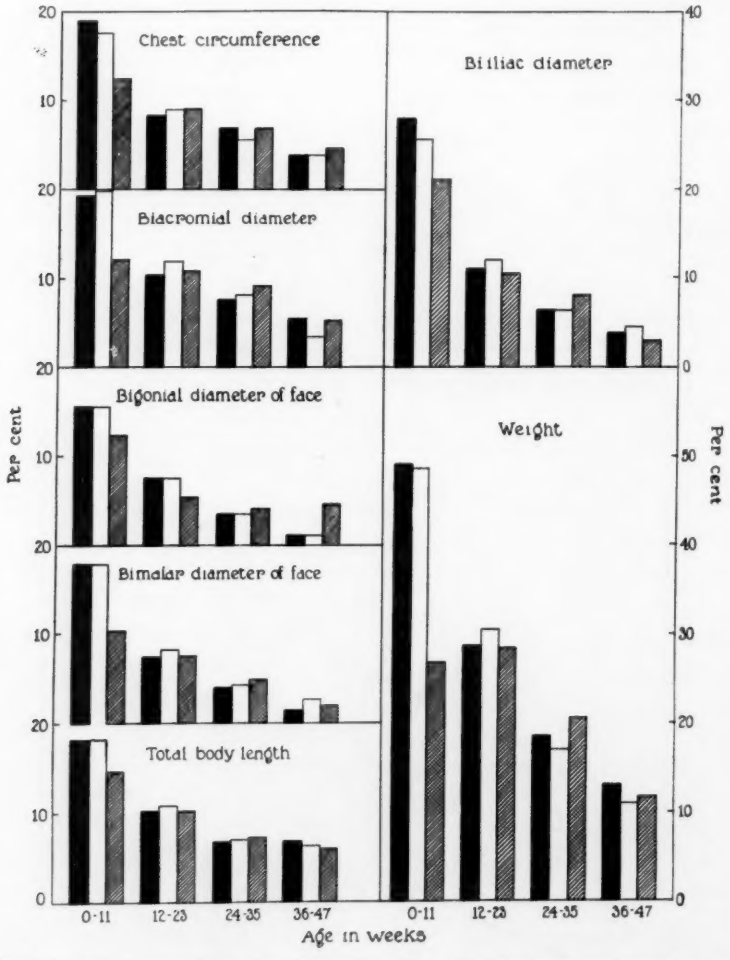

Chart 6.—The percentage growth rates for various body dimensions by twelve week periods during the first forty-eight weeks of life. The solid columns represent the group at the Fifth Avenue Hospital; the blank columns, the supervised group at Bellevue Hospital, and the cross-hatched columns, the unsupervised group at the Bellevue Hospital.

twelve weeks of life the total body length grows less rapidly than the biacromial or bi-iliac diameters of the trunk, more rapidly than the bimalar or bigonial diameters of the face and at about the same rate as the

circumference of the chest, yet there is less retardation in the growth of height than in any of these measurements.

COMMENT

The finding in a previous study that infants from an unfavorable social environment not only are shorter and lighter than infants from a more favorable environment but have lateral dimensions significantly smaller in relation to total body length is confirmed. It has been possible, through care, particularly with respect to diet, to improve the growth in height and weight of the infants from the poorer group and to change their body proportions to those approximating infants from a more favorable environment, thereby eliminating as factors influencing the differences in body build a large number of variables implied in the social environment.

It seems reasonable to assume that the improvement in growth induced in the poorer group through the agency of the well baby clinic was due to better dietary management. Through frequent visits to the clinic during the early months of life, dietary errors were promptly corrected, and requirements carefully adjusted for the individual infants. Urging isolation of young infants may also have had some influence on limiting infections of the upper respiratory tract, which have so severe an influence on nutrition during the first weeks of life.

The nature of the defect in the diet of the unsupervised group can only be conjectured. Most of the infants admitted to Bellevue Hospital receive breast milk or dilutions of cow's milk with sugar. Orange juice is given with fair regularity and cod liver oil rarely. The main defect in the diet appears to be an inadequacy in the energy-yielding substances. The dietary inadequacy is accentuated by the frequency of infections of the upper respiratory tract, which interfere with the administration and retention of the diet. Though accessory foods are given in this group relatively late, the change in body proportions occurs before the twelfth week of life, when accessory foods are frequently not given in large amounts to supervised infants, although the control groups in this series received egg-yolk and vegetable or cereal during the third month of life.

SUMMARY

1. The observation on a group of infants from a poverty-stricken environment that when retardation of growth occurs the retardation is greater for the lateral than for the cephalo-caudal (total body length) dimensions is confirmed.

2. Through supervision in a well baby clinic, the increase in the height and weight of the infants from the poverty-stricken environment has been raised approximately to that of a control group. Coinci-

dentally, there has been a change in the proportions of the lateral dimensions to total body length from a relative "linearity" to that of the control group.

3. The retardation in growth of the group from the poverty-stricken districts occurred entirely within the first twelve weeks of life. Thereafter the groups grew at about the same rate.

4. There is no correlation between the growth rate and the degree of retardation in infancy.

BASAL METABOLISM OF AMERICAN-BORN CHINESE GIRLS AND OF AMERICAN GIRLS OF SAME AGE

CHI CHE WANG, PH.D.
CINCINNATI

In a recent publication Benedict and Meyer [1] reported that the metabolism of eighteen American-born Chinese girls, between the ages of 12 and 22, in Boston was on the average 9.2 per cent lower than the Harris-Benedict or Girl Scout standard and 6.1 per cent below the Aub-Du Bois standard. In conclusion, these authors stated: "Undoubtedly the racial factor plays a less pronounced rôle in the metabolism of the Chinese. Nevertheless, we believe that this present investigation tends to support the earlier observations to the effect that Chinese and Japanese, even though American-born, subsisting in part a modern American life, have a metabolism somewhat lower than Caucasian."

These conclusions of Benedict and Meyer are contrary to the finding of Hawks and me [2] that the basal metabolism of American-born Chinese children in Chicago is entirely comparable with that of American-born Chinese children of the same ages in Boston. However, as I shall show, when the data of the two studies are analyzed it is found that they are in close agreement, and only the conclusions drawn from them are at variance.

COMPARISON OF BASAL METABOLISM OF THE TWO GROUPS OF AMERICAN-BORN CHINESE SUBJECTS

Except for one 12 year old girl, Benedict and Meyer's subjects ranged from 13 to 22 years of age. Consequently, the majority of them had undoubtedly already passed the period of "prepuberty rise" of basal metabolism. On the other hand, with the exception of a 17 year old girl whose energy values were not included in the averages, as is clearly pointed out in the article, none of our subjects had reached puberty. They ranged from 5 to 14 years of age, with an average age of 9 as against 16 for the subjects of Benedict and Meyer. The marked

From the Children's Hospital Research Foundation and the Department of Pediatrics, College of Medicine, University of Cincinnati.

1. Benedict, F. G., and Meyer, M. H.: Chinese J. Physiol. **7**:45, 1933.

2. Wang, C. C., and Hawks, J. E.: Basal Metabolism of Twenty-One Chinese Children Reared or Born and Reared in the United States, Am. J. Dis. Child. **44**:69 (July) 1932.

difference in the ages of the subjects undoubtedly accounts in part for the discrepancy in the conclusions drawn by the different workers.

Although we compared our results with different "standards," our fundamental argument was that the basal metabolism of the Chinese children was within the same range, on any basis of computation, as that of a strictly corresponding group of American children studied in the same laboratory. Thus the average for the Chinese girls was 47.3 calories per kilogram per twenty-four hours, with a range of from 33.6 to 57.3 calories, or 1,195 calories per square meter per twenty-four hours, with a range of from 987 to 1,360 calories. The average for the American girls was 48.8 calories per kilogram per twenty-four hours, with a range of from 35 to 56 calories, or 1,243 calories per square meter per twenty-four hours, with a range of from 1,010 to 1,510 calories.

In order to compare directly values for subjects of the higher age range of Benedict and Meyer's work, in table 1 is given a comparison of the metabolism of four Chinese girls, aged 12, 13, 14 and 17, studied by Hawks and me and the average values for Chinese girls of the same ages studied by Benedict and Meyer. With the exception of the 12 year old girls, the Chicago girls show a slightly lower metabolism than the Boston girls. The actual differences are comparatively slight and the values, on the whole, agree exceptionally well. The contradictory conclusions of the two papers are therefore undoubtedly due to the difference in the normal standards of reference used by the authors.

Stark [3] has discussed the difference in the predicted values of the various standards, with the exception of the Girl Scout standards, and has pointed out that both the Aub-Du Bois and the Harris-Benedict standards are too high for girls between 17 and 20 years of age. The Girl Scout standards, with their 10 per cent correction for sleep, are, in the opinion of the writer, also too high for the average American girl. It is unlikely that all the girls under observation would be sound asleep throughout the test. Consequently, the 10 per cent correction is probably too high. Later in this paper I shall demonstrate clearly that only about 20 per cent of average American girls have a basal metabolism as high as their predicted values.

COMPARISON OF THE BASAL METABOLISM OF AMERICAN-BORN CHINESE GIRLS WITH THAT OF AMERICAN GIRLS OF SAME AVERAGE AGE

In table 3 are given new data on fourteen American girls in Cincinnati, ranging in age from 12 to 20, with an average age of 16, i. e., of about the same age range as the Chinese girls studied by Benedict and

3. Stark, M. E.: J. Nutrition **6**:11, 1933.

TABLE 1.—*Basal Metabolism of American-Born Chinese Girls Observed by Wang and Hawks and by Benedict and Meyer*

Age, Years	Authors	Number of Subjects	Average Weight, Kg.	Average Height, Cm.	Calories per 24 Hours			Percentage of Deviation from Standards								
								Calories per 24 Hours				Calories per Sq.M. per 24 Hours				Calories per Kg. per 24 Hours, Benedict
								Benedict-Talbot				Benedict-Talbot				
					Total	Per Kg.	Per Sq.M.	Referred to Age	Referred to Weight	Girl Scout	Dreyer	Referred to Age	Referred to Weight	Aub-Du Bois	Boothby-Sandiford	
17	Wang and Hawks	1	47.0	145	1,184	25.2	818	.....	— 3.2	—13.9	—10.2	.....	.....	—14.8	— 9.1	+15.6
	Benedict and Meyer	4	47.0	153	1,183	25.3	839	.....	— 5.2	—14.0	—12.6	.....	.....	—12.7	— 6.8	+16.1
14	Wang and Hawks	1	34.6	137	1,162	33.6	986	+ 1.5	+ 0.2	—15.5	+ 0.1	+ 3.0	+ 6.2	+ 2.7	+ 0.2	+ 1.8
	Benedict and Meyer	2	38.8	152	1,325	34.4	1,023	+16.7	+10.8	— 3.7	+ 8.0	+ 7.1	+10.7	— 0.8	+ 3.9	+31.3
13	Wang and Hawks	1	27.6	133	1,014	36.7	1,001	— 7.8	+ 2.4	—26.3	— 3.2	+ 4.3	+ 6.1	+ 4.3	— 0.7	+ 8.9
	Benedict and Meyer	3	30.6	145	1,182	38.8	1,041	+ 7.5	+14.1	—14.0	+11.9	+ 8.4	+11.1	— 3.2	+ 3.3	+35.7
12	Wang and Hawks	1	34.4	147	1,284	37.3	1,094	+21.7	+11.0	— 6.6	+ 8.6	+13.7	+17.8	+14.0	+ 6.0	+ 8.7
	Benedict and Meyer	1	35.8	152	1,269	35.4	1,007	+20.3	+ 7.5	— 7.7	+ 5.2	+ 4.6	+ 8.7	— 6.3	— 2.5	+14.2

TABLE 2.—*Average Basal Metabolism of Eighteen American-Born Chinese Girls in Boston*

Subject	Age, Years	Weight, Kg.	Height, Cm.	Calories per 24 Hours			Percentage of Deviation from Standards									
							Calories per 24 Hours					Calories per Sq.M. per 24 Hours				Calories per Kg. per 24 Hours, Benedict
							Benedict-Talbot		Harris-Benedict or Girl Scout	Dreyer	Stark	Benedict-Talbot		Aub-Du Bois	Boothby-Sandiford	
				Total	Per Kg.	Per Sq.M.	Referred to Age	Referred to Weight				Referred to Age	Referred to Weight			
A	22	49.9	158	1,182	23.7	793	.....	— 6.0	—10.6	—10.0	— 3.5	.....	.....	—10.7	— 9.5	.....
B*	21	62.1	164	1,672	26.9	995	.....	.....	+15.0	+13.4	+21.7	.....	.....	+12.1	+13.6	.....
C	19	39.9	155	1,199	30.0	895	.....	— 2.0	—12.8	+ 0.2	+ 8.1	.....	— 2.9	— 1.9	+ 2.2	+37.6
D	18	45.1	159	1,223	27.1	855	.....	— 1.5	—11.1	— 4.6	+ 3.8	.....	.....	— 6.3	— 3.7	+24.3
E	17	46.9	159	1,136	24.2	779	.....	— 9.0	—17.4	—13.7	— 5.1	.....	.....	—18.9	—13.4	+11.0
F	17	44.0	150	1,024	23.3	753	.....	—17.3	—25.5	—19.7	— 9.9	.....	.....	—21.6	—16.3	+ 6.9
G	17	43.6	148	1,335	30.5	998	.....	+ 8.0	— 2.9	+ 5.1	+18.6	.....	.....	+ 4.0	+10.9	+39.9
H	17	53.3	155	1,237	23.2	825	.....	— 2.4	—10.0	—11.9	— 1.2	.....	.....	—14.1	— 8.3	+ 6.4
I	16	53.3	157	1,320	24.8	869	.....	+ 4.1	— 4.0	— 6.8	.....	.....	.....	— 9.5	— 6.0	+13.2
J	16	39.9	151	1,205	30.2	920	.....	— 1.6	—12.4	— 1.6	.....	.....	— 0.2	—10.9	— 0.4	+37.9
K	16	39.9	156	1,079	27.0	805	.....	—11.8	—21.5	—11.9	.....	.....	—12.7	—22.0	—12.9	+23.3
L	15	39.0	151	1,435	36.8	1,104	.....	+17.7	+ 4.4	+17.5	.....	.....	+19.6	+ 7.0	+16.4	+54.6
M	14	41.7	152	1,345	32.3	1,003	+18.5	+ 9.3	— 2.2	+ 5.5	.....	+ 5.0	.....	— 2.8	+ 1.9	+23.3
N	14	35.8	151	1,304	36.4	1,043	+14.9	+12.3	— 5.2	+10.4	.....	+ 9.2	+12.6	+ 1.1	+ 6.0	+38.9
O	13	28.6	141	1,202	42.0	1,103	+ 9.3	+18.8	—12.6	+12.8	.....	+14.9	+17.2	+ 2.6	+ 9.4	+46.9
P	13	31.3	147	1,039	33.2	903	— 5.5	— 3.4	—24.4	— 6.8	.....	— 5.9	— 3.4	—16.0	—10.4	+16.1
Q	13	31.8	148	1,306	41.1	1,116	+18.7	+20.2	— 5.0	+16.2	.....	+16.3	+19.5	+ 3.8	+10.7	+43.7
R	12	35.8	152	1,269	35.4	1,007	+20.3	+ 7.5	— 7.7	+ 5.5	.....	+ 4.6	+ 8.1	— 6.3	— 2.4	+14.2
Average	16	42.3	153	1,251	30.5	933	+12.7†	+ 2.5	— 9.2	— 0.06	+ 4.1§	+ 7.4†	+ 6.5‡	— 6.1	+ 0.7	+27.4

* Subject had "heart trouble."
† Average of 6.
‡ Average of 9.
§ Average of 8.

TABLE 3.—*Basal Metabolism of Fourteen American Girls in Cincinnati*

Subject	Age, Years	Weight, Kg.	Height, Cm.	Calories per 24 Hours: Total	Calories per 24 Hours: Per Kg.	Calories per 24 Hours: Per Sq.M.	Percentage of Deviation from Standards: Calories per 24 Hours: Benedict-Talbot: Referred to Age	Benedict-Talbot: Referred to Weight	Harris-Benedict or Girl Scout	Dreyer	Stark	Calories per Sq.M. per 24 Hours: Benedict-Talbot, Referred to Age	Aub-Du Bois	Boothby-Sandiford	Calories per Kg. per 24 Hours, Benedict, Referred to Age
P. M.	20	45.3	163	1,260	27.9	866	.....	+ 1.5	— 2.5	— 0.5	+ 5.6	.....	— 2.5	— 1.1	+28.0
M. F.	18	52.6	157	1,330	25.3	881	.....	+ 5.1	— 3.3	— 4.0	+ 6.3	.....	— 8.2	— 1.0	+16.1
D. R.	18	44.2	161	1,285	29.2	898	.....	+ 3.8	— 6.5	+ 1.3	+ 9.5	.....	— 6.5	+ 1.1	+34.0
M. S.	17	62.8	154	1,428	22.9	878	.....	.....	+ 3.9	— 6.3	+ 5.8	.....	— 8.5	— 2.6	+ 5.1
R. P.	17	57.4	166	1,285	22.5	787	.....	+ 0.3	— 6.7	—11.8	.....	.....	—18.0	—12.7	+ 3.0
H. F.	16	44.5	151	1,239	27.9	907	.....	— 0.1	— 9.9	— 4.3	.....	.....	— 5.5	— 2.0	+27.2
I. G.	16	49.2	164	1,424	28.9	938	.....	+13.4	— 3.6	+ 4.7	.....	.....	— 2.3	+ 1.6	+31.9
E. S.	16	52.1	161	1,153	22.3	756	.....	— 8.9	—16.1	—17.6	.....	.....	—26.7	—18.3	+ 1.6
K. K.	15	60.8	166	1,511	24.9	902	+33.1	.....	+ 9.9	— 0.9	.....	— 5.1	—12.6	— 4.8	— 0.4
F. B.	15	40.4	157	1,271	31.5	974	+12.0	+ 3.2	— 7.6	+ 2.0	.....	+ 2.5	— 5.6	+ 2.7	+25.8
B. S.	14	48.2	156	1,359	28.2	936	+23.5	+ 8.6	— 1.2	— 0.8	.....	— 2.0	— 9.3	— 4.9	+ 7.6
D. C.	14	36.7	154	1,193	32.6	974	+ 8.5	— 0.1	—13.2	— 0.5	.....	+ 2.0	— 5.6	— 1.0	+18.8
R. F.	13	45.6	163	1,300	28.5	888	+20.9	+ 4.6	— 5.5	— 4.3	.....	— 7.5	—17.4	—11.9	— 0.4
L. B.	12	29.0	137	1,044	35.1	1,018	+ 0.4	+ 2.3	—24.1	— 3.5	.....	+ 5.6	— 5.3	— 1.5	+21.0
Average	16	47.8	158	1,291	27.7	900	+16.4*	+ 2.8	— 6.2	— 3.3	+ 4.5†	— 0.8‡	— 9.6	— 4.0	+15.7

* Average of 6.
† Average of 4.
‡ Average of 6.

Meyer. These American girls were decidedly taller and heavier than the Chinese girls. Their average weight was 47.8 Kg. and their height 158 cm., as against 42.3 Kg. and 153 cm. for the Chinese girls. When the basal metabolism values are expressed in terms of total calories per twenty-four hours, the average value for the Chinese girls is 3 per cent lower than that for the American girls, but when the calculations are expressed on the basis of body units, either weight or surface area, the Chinese girls have a higher metabolism than the American girls. Thus, the average values for the Chinese girls are 30.5 calories per kilogram or 933 calories per square meter per twenty-four hours, while the corresponding values for the American girls are 27.7 and 900 calories.

In the nine comparisons made with various standards, only three of the average metabolism values for the Chinese girls are lower than the predicted values, while five of those for the American girls are below. The Chinese girls show a lower basal metabolism than the American girls in only two instances, i. e., with Harris-Benedict or Girl Scout standard and with the standard of Benedict and Talbot, total calories per twenty-four hours referred to age. The average metabolism value for the Chinese girls is 9.2 per cent below the Harris-Benedict or Girl Scout standard and 12.7 per cent above the Benedict-Talbot value, while the average value for the American girls is 6.2 per cent below the Harris-Benedict and 16.4 per cent above the Benedict-Talbot standard. The difference between the basal metabolism values for the two groups of girls is very slight, within 1 per cent, when Stark's standard, or the standard of Benedict and Talbot, either total calories per twenty-four hours referred to weight or calories per square meter per twenty-four hours referred to weight, is used. In all other comparisons the Chinese girls had a higher metabolism than the American girls. Thus, using the Aub-Du Bois standard, the average metabolism of the Chinese girls is — 6.1 per cent while that of the American girls is — 9.6 per cent. With Benedict's standard, calories per kilogram per twenty-four hours, the basal metabolism is + 27.4 per cent for the Chinese and + 15.7 per cent for the American girls; the corresponding values with Dreyer's standard are — 0.06 and — 3.3 per cent, and those with the Boothby-Sandiford standard are + 0.7 and — 4 per cent.

COMPARISON OF BASAL METABOLISM OF AMERICAN-BORN CHINESE GIRLS WITH THAT OF SIXTY-SIX AMERICAN GIRLS FROM THREE SECTIONS

The basal metabolism values for 52 American girls between the ages of 12 and 20 taken from the data published by Tilt [4] of Florida and

4. Tilt, J.: J. Biol. Chem. **86**:635, 1930.

MacLeod [5] of New York were recalculated and compared, together with the data for the Cincinnati girls, with nine normal standards. The averages of the values for different age groups and of those for the subjects from each of the three sections, as well as the averages for the total of 66 American girls, are given in table 4. The average age of the sixty-six American girls was the same as that of the American-born Chinese girls of Benedict and Meyer's series. Their average basal metabolism expressed in terms of total calories per twenty-four hours is higher than that of the American-born Chinese girls but lower than that of the Cincinnati girls. When the values are expressed on the basis of either body weight or surface area, the metabolism of this group becomes even lower than that of the Cincinnati girls. Consequently it is much lower than that of the American-born Chinese girls. Thus, the average basal metabolism of the sixty-six American girls is 27 calories per kilogram per twenty-four hours, or 885 calories per square meter per twenty-four hours, while the corresponding values for the American-born Chinese girls are 30.5 and 933 calories. On comparison of these values with the 9 normal standards, except in the case of the Harris-Benedict or Girl Scout standards, the average basal metabolism of the sixty-six American girls was lower than that of the American-born Chinese girls. The values are all slightly lower than those for the Cincinnati group.

Of the whole group of sixty-six American girls, only twelve, or 18.5 per cent, have a higher basal metabolism than the predicted value according to either the Harris-Benedict or the Girl Scout standards, with a 10 per cent correction for sleep. The average deviation for the twelve girls is only + 5.3 per cent. On the other hand, 81.5 per cent of the girls have an average difference of — 10.3 per cent, which is slightly lower than that of the American-born Chinese girls comparing with this standard. Their value is — 9.2 per cent. According to this standard, therefore, the metabolism of 81.5 per cent of the average American girls is slightly lower than that of the American-born Chinese girls studied by Benedict and Meyer.

With the Aub-Du Bois standards only three, or 1.4 per cent, of the sixty-six American girls give a higher value than the predicted figure. The rest of the girls, 98.6 per cent, show an average deviation from the standard of — 12.2 per cent, as against — 6.1 per cent, the corresponding value for the American-born Chinese girls. Thus, according to Aub-Du Bois standards, 98.6 per cent of the average American girls between 12 and 22 years of age have a lower basal metabolism than the group of American-born Chinese girls in Boston.

5. MacLeod, G.: Studies of the Normal Basal Energy Requirement, New York, Columbia University Press, 1924.

TABLE 4.—*Average Basal Metabolism of Sixty-Six American Girls*

Author	Number of Subjects	Location	Age, Years	Weight, Kg.	Height, Cm.	Calories per 24 Hours			Percentage of Deviation from Standards								
									Calories per 24 Hours					Calories per Sq.M. per 24 Hours			Calories per Kg. per 24 Hours, Benedict, Referred to Age
									Benedict-Talbot		Harris-Benedict or Girl Scout	Dreyer	Stark	Benedict-Talbot, Referred to Age	Aub-Du Bois	Boothby-Sandiford	
						Total	Per Kg.	Per Sq.M.	Referred to Age	Referred to Weight							
Tilt.....	7	Florida	20	52.5	160	1,218	23.2	793	.....	— 3.8	— 9.5	—11.1	— 3.3	.....	—12.0	— 9.4	+ 6.3
	7		19	55.5	160	1,245	22.4	800	.....	— 4.7	—10.3	—11.8	— 3.8	.....	—12.3	— 6.8	+ 2.9
	5		18	53.5	159	1,252	23.6	819	.....	— 0.9	— 9.6	—10.2	— 1.1	.....	—10.2	— 3.7	+ 8.1
	3		17	51.0	157	1,163	23.0	786	.....	— 9.8	—16.3	—15.4	— 5.9	.....	—16.7	—14.1	+ 5.5
Average for Florida	22	Florida	19	53.5	159	1,227	23.0	802	.....	— 4.3	—10.7	—11.9	— 3.3	.....	—12.3	— 7.9	+ 4.5
MacLeod	10	New York	14	45.8	156.5	1,249	26.9	870	+10.1	+ 0.8	— 9.1	+ 3.3	.....	— 8.9	—15.7	—11.6	+ 2.8
	10		13	42.5	154.1	1,361	31.6	993	+23.7	+11.0	— 1.1	+ 5.9	.....	+ 3.4	— 7.7	— 0.9	+10.4
	10		12	41.4	150.8	1,283	30.4	957	+21.6	+ 5.6	— 6.7	— 1.1	.....	— 0.6	—11.0	— 7.3	— 2.0
Average for New York	30	New York	13	43.2	154.1	1,298	29.6	940	+18.5	+ 5.8	— 5.6	+ 2.7	.....	— 2.1	—11.5	— 6.6	+ 3.7
Average for Cincinnati	14	Cincinnati	16	47.8	158	1,291	27.7	900	+16.4	+ 2.8	— 6.2	— 3.3	+ 4.5	— 0.8	— 9.6	— 4.0	+15.7
Average for three sections	66	Florida, New York, Cincinnati	16	47.6	158	1,273	27.0	885	+18.1	+ 2.2	— 7.3	— 3.4	— 1.8	— 1.8	—11.4	— 6.6	+ 6.9

Table 4 shows that the basal metabolism values for the girls of different age groups as well as those for girls from different sections demonstrate a greater diversity than the values for girls of the two races. Thus, the average basal metabolism of the 13 year old group is markedly higher than that of any other age group, while the 17 year old group has the lowest value. With values given in terms of total calories per twenty-four hours the difference between the two extreme groups is 17 per cent, while the difference in the values for the two races is only 3 per cent, as has been pointed out. The marked difference between the two age groups is demonstrated not only in the total calories per twenty-four hours, but in values expressed on the basis of both body weight and surface area. Thus, the 17 year old group has a basal metabolism of 23 calories per kilogram of 786 calories per square meter per twenty-four hours as against 31.6 and 993 calories, respectively, for the 13 year old group.

The girls from different sections of the United States also demonstrate a greater diversity in their basal metabolism than those belonging to the two races.

The basal metabolism values of the New York girls are slightly higher than those of the Cincinnati girls and decidedly higher than those of the Florida group, there being an increase of 6 per cent on the basis of calories per twenty-four hours. When the values are expressed in terms of body units, the difference becomes much greater, 28 per cent for body weight and 17 per cent for surface area.

CONCLUSION

Judging from the foregoing comparisons, it is difficult to conclude that orientals have a lower basal metabolism than occidentals. The studies conducted on the two groups of American-born Chinese subjects have certainly failed to show any difference between their basal metabolism and that of Americans of the same age range.

There is no doubt that there are at present, especially for children, too many normal standards of wide variation, and the danger of comparing basal metabolism data against "prediction standards" is becoming more and more apparent. In my opinion, it is therefore unsafe to compare the basal metabolism of two groups of subjects, unless the work is conducted side by side or the values are compared with the same standards.

PRELIMINARY REPORT OF THE FELS FUND

STUDY OF FETAL ACTIVITY

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There has been a somewhat general tendency to consider birth as the introduction of the period in which environment may be assumed to be a factor influencing the growth and development of the human organism. Thus most of the vast amount of study on the physical and mental development of children has begun with birth, more or less completely neglecting the possible influence of environment during the period of intra-uterine development.

While there are many excellent anatomic studies of the development of the human fetus, little consideration has been given to its behavior or to environmental factors which might conceivably influence it. Many investigators have considered birth as the beginning of mental development and of consciousness. Yet we are all familiar with the fact that in cases of prematurity in which birth occurs at a fetal age of about 7 months learning and response to stimuli develop rapidly and are well established long before the infant has reached the age at which it normally would be born. Certain persons who do not wish their names to be mentioned are working along the lines of Minkowski. They have attempted to stimulate mechanically fetuses obtained from therapeutic abortions. They have been successful in eliciting a response to mechanical stimuli in fetuses 2 months of age. Whereas these facts prove nothing regarding the ability of the fetus to learn or to respond to stimuli during intra-uterine life, nevertheless, they are suggestive. They indicate, even though they do not prove, that certain factors in prenatal environment may influence the behavior of the unborn child quite as definitely as other environmental factors may influence the behavior of the new-born child.

Peiper [1] called attention to the need for study of the behavior of the human fetus before birth. He found evidence that during the tenth lunar month of intra-uterine development the human fetus is capable not only of perceiving certain sounds but also of responding to these auditory stimuli by sudden and convulsive movement. He

1. Peiper, A.: Sinnesempfindungen des Kindes vor seiner Geburt, Monatschr. f. Kinderh. **29**:236, 1925.

found further that after such a stimulation and response there followed a period of several minutes during which an auditory stimulation was not followed by movement. He believed that the existence of this refractory period indicates that the fetus is capable of registering sensory impressions. As a part of his experimental work on the ability of new-born infants to perceive auditory stimuli he attempted to elicit a response to such stimulation in six infants less than 1 hour of age. Four responded to the stimuli by changes in the respiratory rhythm or by convulsive movements. Of the other two, one was so restless that it was useless for experimental purposes of this sort, and the other did not respond.

Peiper also called attention to the amount and severity of fetal movement felt by some women while listening to concerts. Forbes and Forbes [2] mentioned the case of a woman who while attending a concert experienced a sensation of great fetal activity every time the audience applauded. In experiments with a series of seventy new-born children from 6 hours to 14 days of age, Canestrini [3] found that none remained inactive in the presence of an adequate auditory stimulus. Preyer,[4] on the other hand, concluded that because the middle ear contains no air at birth and because the external ear is closed sound is imperceptible to the fetus. However, since we know that hearing by osseous condition is possible even in persons with a complete destruction of the membrana tympani and ossicles, we are probably justified in accepting the affirmative experimental results of Peiper and Canestrini. Ray [5] has described a device for recording fetal movement and has attempted to condition the human fetus by pairing certain auditory stimuli with a closely following mechanical one.

Although our own work dealing with the behavior of the human fetus in utero is only well begun, it has seemed desirable to make some statement of the direction of our endeavors and of such information as we have collected. We hope that others may be stimulated to undertake work in the same field, since we feel that it is one which has been unfortunately neglected.

The fields of investigation of fetal behavior in which we have been engaged might be classified as follows: (1) relationship of fetal movement to certain factors of the mother's life, such as emotions,

2. Forbes, H. S., and Forbes, H. B.: Fetal Sense Reactions: Hearing, J. Comp. Psychol. **7**:353, 1927.

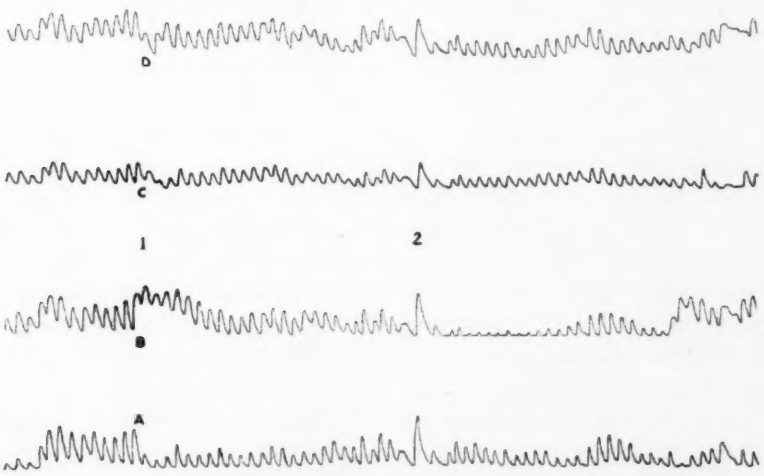
3. Canestrini, S.: Ueber das Sinnesleben des Neugeborenen, Berlin, Julius Springer, 1913.

4. Preyer, W.: Spezielle Physiologie des Embryo, Leipzig, T. Grieben, 1885, p. 481.

5. Ray, Wilbert S.: A Preliminary Report of a Study of Fetal Conditioning, Child Development **3**:175, 1932.

fatigue, position of the body and ingestion of food; (2) fetal response to external stimuli, both auditory and mechanical; (3) possibility of conditioning the fetus; (4) cardiac and respiratory activity of the fetus and their relationship to the body function of the mother.

An apparatus for recording fetal movement and differentiating it from extraneous movements has previously been described by us.[6] This apparatus, while it resembles the apparatus used by Hicks[7] and that used by Ray,[5] in that it utilizes tambours to actuate the recording pens, is different in several respects. Instead of a single tambour placed over a very small area of the abdomen, it utilizes four rubber sacs filled with air, covering almost the entire abdomen. These sacs are



Sample record, showing fetal movement at *1* and a breathing disturbance, such as sighing, at *2*. Whereas one pen, *B*, moves in the opposite direction from the others when fetal movement is recorded, during breathing without fetal movement all the pens move in the same direction at one time.

held in place by a thin plaster of paris cast. Each sac is connected with a delicately adjustable tambour which in turn actuates a recording pen. The record is made on a strip of paper 14 inches (35.56 cm.) wide which is driven by an electrically powered brass drum. The records of the four quadrants of the abdomen make it relatively easy to differentiate fetal movements from respiratory movements, since the respiratory movements produce a synchronous swing of the recording pens,

6. Sontag, L. W., and Wallace, R. F.: An Apparatus for Recording Fetal Movement, Am. J. Psychol. **45**:517, 1933.

7. Hicks, Braxton: On Recording Fetal Movements by Means of the Gastrograph, Tr. Obst. Soc. London **22**:134, 1880.

while fetal movements produce a divergence of at least two of the pens,[8] as shown in the tracing.

FACTORS IN THE MOTHER'S LIFE INFLUENCING MOVEMENT OF THE FETUS

We have frequently heard the statement made by expectant mothers that any sudden feeling of fear or of anger produces an almost immediate and marked increase in the number and violence of the fetal movements. This statement has been made so frequently that we are convinced that such a belief is rather common among women. Recently we had an excellent opportunity to observe this phenomenon. During the last three lunar months of pregnancy a woman experienced terrific fear on at least three different occasions due to the periods of mania of an insane husband. Although she was never actually injured by him the woman became so frightened by these recurrences of her husband's uncontrolled behavior that on these occasions she sought refuge in a friend's home. On all three of these occasions she complained of being unable to sleep because of the violence and persistence of fetal activity. On the days following these incidents she complained of a marked soreness of the abdominal muscles, which she attributed to the violence of the fetal movement. She was seen by one of us during one of the periods of fear. At that time the fetus seemed to be undergoing a series of convulsive movements, one or another of the small parts almost constantly causing sharp prominences of the maternal abdomen. Although these observations were made without the use of the fetal movement recorder, the patient was observed on many occasions when she was not in an abnormal emotional state. On those occasions the fetal activity was no more pronounced than that usually observed during the eighth or ninth month of pregnancy and was not at all comparable to that observed during the period of fear.

We had an opportunity to take records of fetal movement on one patient during a period of rather severe emotional stress which resulted from a quarrel with a roommate. The unsettled emotional state continued for approximately three weeks, during which the patient experienced frequent periods of anger, indignation, consternation, fear, and anxiety. During this period, the daily thirty minute records which were made showed activity during approximately 70 per cent of the time as compared with 35 per cent of the time preceding and 50 per cent of the time following this period.

In answer to a question regarding the effect of fatigue on the amount of fetal movement, it was the almost universal opinion among about

8. This action is explained in more detail in the recently published description of the apparatus.

fifty women questioned that they experienced the sensation of much more violent movements as well as more frequent ones when severely fatigued. The mechanism of this influence on fetal activity is at present unknown. It is conceivable that it may be the same as that which appears to influence fetal movement during periods of fright. How much of the impression of increased movement after fatigue is actually due to a greater amount of activity of the fetus and how much of it is the result of an increased sensitivity on the part of the mother, due to fatigue, is questionable. One must think of changes in the secretion of the ductless glands, the accumulation of waste products such as lactic acid, changes in the tonicity of the uterine or abdominal muscles, and probably many other factors as possible mechanisms influencing fetal activity.

We have had no opportunity to estimate by means of the fetal movement recorder the amount of fetal movement before fatigue as compared with that during periods of fatigue because of a lack of patients who were available during periods of severe fatigue. We observed one patient who believed that her sensation of fetal movement was markedly decreased during the time she spent in a reclining position. Our records show that a relatively slight amount of movement was present during these periods of reclining, but unfortunately it was not possible to make records for comparison while the patient was in the erect position. There was considerable difference between this woman's sensations of movement when she was lying on her side and on her back. Lying on the side was accompanied by more movement than the other position.

We are at present collecting data on the relationship of ingestion of food to fetal movement.

RESPONSE TO EXTERNAL AUDITORY AND MECHANICAL STIMULATION

By means of the fetal movement recorder we have attempted to obtain a roughly quantitative estimate of fetal movement under certain conditions of stimulation. Ideally, the unit of measurement of fetal movement might be considered as the erg, but under the conditions of the experiment this must remain an unpractical ideal. However, the presence or absence of movement can readily be judged with a fair degree of accuracy either by placing the hands on the abdomen of the mother or by examining the records of the apparatus for registering fetal movement. This differentiation offers a quantitative means of estimating fetal activity. It does not, of course, give any measure of the energy expended in one movement as compared with that expended in another. Nevertheless it is satisfactory for the purpose of studying the response to stimuli. Following stimulation of the fetus with 120

vibrations per second it is easy to demonstrate that movement does occur.[9] In order to establish the fact that these movements are actually a response to stimulation rather than a result of chance, we have attempted to consider quantitatively the movement immediately following stimulation as compared with that found in random periods of observation. By applying our criterion of movement or no movement to the first fifteen second period after stimulation, we have secured the following results: 1. In seven series of stimulations of one subject, twenty-nine stimuli being presented at one minute intervals, in every case but one, there was a fifteen second period immediately following stimulation which contained one or more fetal movements; that is, there was activity in 97 per cent of these periods. In the three fifteen second periods following each of the first periods there was activity in respectively 59, 17 and 17 per cent, or an average of 32 per cent of the periods; roughly there were three times as many periods of activity immediately following stimulation as for the average of the three remaining periods. 2. In two series of stimulations of two different subjects in which the stimulus was presented at two minute intervals, we found movement in 92 per cent of the fifteen second periods immediately following stimulation and in 23 per cent of the periods not preceded by stimulation. 3. In two other series in which stimulation was given at three minute intervals there was activity in 94 per cent of the periods immediately following stimulation and in 37 per cent of the other periods. 4. Finally, in a series in which stimuli were presented at intervals of five minutes there was activity in 80 per cent of the periods immediately following stimulation whereas but 49 per cent of the remaining periods showed activity. Further data on response to stimuli are being collected, and when a sufficient volume has been assembled the calculation of the probable error of the difference between stimulated and unstimulated periods will give a better evaluation of this point. It is interesting to note that although Ray attempted to condition the fetus to respond to a stimulus of 120 vibrations per second, we are certain that the four fetuses on which we tried the experiment responded

9. The stimulation in these experiments was made by an apparatus constructed from Ray's description.[5] It consisted of an electric bell from which the gong had been removed and in which the make and break contact was short circuited. Thus when the bell was energized with 60 cycle alternating current from a transformer, a vibration of 120 double vibrations per second was secured. This was made to tap against a wooden block placed on the abdominal surface of the mother near the head of the fetus. When the 384 double vibration stimulus was applied, a tuning fork was sounded on the wooden block. That these sounds carried through to the abdomen was demonstrated by placing the stethoscope against the abdominal surface, on the opposite side from that to which the stimulus was applied. No difficulty was encountered in hearing clearly the vibration of the tuning fork.

without being conditioned. It is possible that this difference in results is due to a difference in the application of the stimuli, since Ray did not use the wooden block against the maternal adbomen as we did.

In regard to the refractory period mentioned by Peiper [1] and by Ray,[5] we observed that a response was made to a second stimulation presented immediately following the cessation of activity from the preceding stimulation—less than fifteen seconds in many cases. However, if stimulation was continued for several trials, even though they were fully a minute apart, after from four to ten trials the latent period set in, and no response to several attempts at stimulation was elicited. More observations of the phenomenon are being made. An attempt to elicit a response to a vibratory stimulus of 384 vibrations per second met with no success.

CONDITIONING

On the theory that the frequency of 384 vibrations per second might be perceptible to the fetus, though not irritating it sufficiently to produce convulsive movements, we decided to use this vibratory frequency in an attempt to condition the fetus. The stimuli were paired, the higher frequency being used first; the total number of stimulations amounted to seventy-one. After the paired stimuli had been applied twenty-one times at intervals of one minute, during which responses were consistently made by the fetus, the vibrations of lower frequency were discontinued, and an attempt was made to elicit a response to the higher frequency only. No more fetal movement was apparent on the record of this last series of stimulations than was observed when the high frequency was first used alone. The remaining fifty times these stimuli were paired in shorter series, and, likewise, no increased response to 384 vibrations was noted. From this we conclude that in our experiment no conditioning took place. Whether this is due to an inability of the fetus to be conditioned or to a lack of perception of the frequency of 384 vibrations per second is still an open question.

CARDIAC RATE AND RESPIRATORY MOVEMENTS

We have collected to date more than ten thousand samplings of cardiac rate during the course of our study of four patients. These data have been secured by determining with the aid of a stop-watch how many seconds and tenths of seconds elapse during the counting of ten beats. We have found a tremendous variability in the rate of the fetal heart, not only from day to day and week to week, but from hour to hour. The material we have gathered is now being arranged statistically in an effort to determine whether there is a significant correlation to any such factor as maternal fatigue, ingestion of food and emotion. The results of this

work are not yet available. A study of the nature and causes of the fetal respiratory movements described by Ahlfeld [10] is also being carried on.

SUMMARY

Attention has been called to the desirability of a more extensive interest in the behavior of the human fetus. A description of the work of the Samuel S. Fels Fund on fetal activity is presented, and the following points are emphasized: (1) relationship of fetal activity to such factors as variations in maternal emotion, maternal ingestion of food, maternal and fetal position and maternal fatigue; (2) the fetus' response or lack of response to certain stimuli and the ensuing refractory period; (3) the possibility of conditioning the human fetus; (4) the relationship of fetal cardiac rate and prenatal respiratory movements to certain physical and emotional factors in the mother.

10. Ahlfeld, Friedrich: Verhandl. d. deutsch. Gesellsch. f. Gynäk. **2**:203, 1888.

FACTORS INFLUENCING THE UTILIZATION OF CALCIUM AND PHOSPHORUS OF COW'S MILK

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One of the major problems in the use of cow's milk for infant feeding has been the physical character of the curd. This phase of the subject has been stressed repeatedly by Brennemann,[1] and the various methods for modifying the curd have been utilized clinically with good results. The three main factors concerned with the type of curd formed from cow's milk in the infant's stomach are casein, rennin and calcium ions. When cow's milk is modified for infant feeding, one or all of the three factors are utilized in the methods of dilution with water or a solution of a protective colloid such as cereal water, addition of rennin, treatment with heat and acidification. Other methods, such as precipitating calcium ions by the addition of alkali (solution of calcium hydroxide and sodium bicarbonate) or forming a complex calcium salt by adding sodium citrate, are seldom used today.

Recently, the attention of the medical profession has been called to a natural "soft curd" milk which may be obtained from certain cows. In contrast to the tough curd formed from ordinary raw cow's milk this milk forms a softer curd on the addition of rennin. The first observations of this phenomenon were made by Buckley [2] and Washburn and Jones.[3] More detailed investigations have been carried out recently by Hill,[4] Espe and Dye[5] and Morris and Richardson.[6] The clinical results of Morris and Richardson indicated that because of variability in

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From the Department of Pediatrics, College of Medicine, University of Illinois.

1. Brennemann, J.: The Curd and the Buffer in Infant Feeding, J. A. M. A. **92**:364 (Feb. 2) 1929.

2. Buckley, S. S.: Maryland Agric. Exper. Stat. Bull. 184, 1914.

3. Washburn, R. M., and Jones, C. H.: Vermont Agric. Exper. Stat. Bull. 195, 1916.

4. Hill, R. L.: Utah Agric. Exper. Stat. Bull. 227 (June) 1931.

5. Espe, D. L., and Dye, J. A.: Effect of Curd Tension on the Digestibility of Milk, Am. J. Dis. Child. **43**:62 (Jan.) 1932.

6. Morris, M., and Richardson, G. A.: The Production and Use of Soft Curd Milk, J. Pediat. **3**:449, 1933.

the production and the lack of superior results when used in comparison with other accepted formulas natural soft curd milk did not warrant special production.

Lyman, Browne and Otting [7] recently reported their results with a method by which ordinary raw cow's milk can be changed to milk which when acted on by rennin produces a soft, fine, flocculent curd. They reasoned that since calcium ions must be present for the curdling of the milk by rennin, it should be possible to produce a soft curd milk from ordinary cow's milk by the removal of some of the calcium ions. Their methods consist of a process of base exchange which results in a readjustment of the salts (chiefly calcium) of the milk. In their first experiments they passed milk through an artificial zeolite (sodium-aluminum silicate). In each trial the milk so treated formed a dense curd with the addition of rennin. Since the amount of calcium removed by this method was small, they decided to increase the amount of soluble calcium by acidification with citric acid before treatment with the zeolite. It was found that previous acidification to about 0.3 per cent greatly facilitated the removal of calcium by the sodium-aluminum silicate (zeolite) and that the resulting product did not form a visible curd with the addition of rennin. The amount of calcium removed from the milk was about 20 per cent. The treatment of the acidified milk by base exchange adjusted the p_H to that of ordinary cow's milk and did not alter the soft flucculence of the curd.

Milk treated by the process of base exchange was made available to us for clinical investigation. The results indicated that infants fed this milk compared favorably with those fed other accepted formulas. A detailed report of this clinical study will be the subject of a separate communication. In this phase of the investigation we are especially concerned with the question of whether the amount of calcium and phosphorus which remained after the treatment of the milk by base exchange would be sufficient to keep a normal infant in a positive calcium and phosphorus balance. A metabolism study was therefore undertaken.

PROCEDURE

Two healthy normal full-term infants were subjects for this study. In the first infant there developed an infection of the upper respiratory tract during the last part of the investigation, so the results were voided. The second subject was a normal Negro male infant 80 days old, weighing 4.5 Kg. at the beginning of the experiment. The study was started on June 27 and ended August 30. The child was in excellent physical condition, and remained afebrile throughout the period of study.

7. Lyman, J. F.; Browne, E. H., and Otting, H. E.: Readjustment of Salts in Milk by Base Exchange Treatment, Indust. & Engin. Chem. **25**:1297, 1933.

The infant was placed on a metabolism frame, and stools and urine were collected quantitatively during three day periods. The fecal periods were marked off with carmine. The stools were dried on a water bath, pulverized and dried to constant weight, and an aliquot portion was taken for analysis. Seventy-two hour specimens of urine were collected and preserved in an icebox until the specimen was complete.

The milk used in the formulas was boiled eight minutes in a double boiler. Boiled tap water was used as a diluent in all formulas, since the routine feeding procedure was being followed. An aliquot portion for each three days' feeding was pooled and samples were taken for analysis. The child received 6 cc. of orange juice per kilogram of body weight daily, so an aliquot sample of the orange juice was added to the pooled specimen of milk taken for analysis. Ten drops of viosterol were given daily throughout the study.

The formulas were calculated on the basis of the minimum requirement of calcium to keep a normal healthy infant in a positive calcium and phosphorus balance. Minimum standards were adopted, since any difference in the milks studied would be shown more definitely on minimum than on optimum quantities. The study consisted of four experimental periods of twelve days each and one of six days, with a day of rest off the metabolism frame between each period. The

TABLE 1.—*Formulas Fed During the Different Experimental Periods per Kilogram of Body Weight*

Period	Milk	Boiled Tap Water, Cc.	Lactose, Gm.	Orange Juice, Cc.
I	Whole boiled cow's milk, 100 cc.	75	8	6
II	Base exchange treated boiled milk, 100 cc.	75	8	6
III	Whole boiled cow's milk and 0.6 Gm. citric acid, 100 cc.	75	8	6
IV	Base exchange treated powdered milk, 13.5 Gm.	175	8	6
V	Whole boiled cow's milk, 100 cc.	75	8	6

new feeding was started during the day of rest. Throughout the study the entire day's feeding was consumed and retained by the infant. Table 1 gives the formulas fed in the different experimental periods.

The calcium content was determined by an adaptation of the Collip [8] modification of the Kramer-Tisdall method, and the phosphorus content was determined by the Youngberg [9] method. Triplicate 100 cc. specimens of urine were dried, ashed, dissolved in hydrochloric acid and diluted to 50 cc. The calcium content was determined on the ash solution, while that of the phosphorus was determined on the urine without ashing. A portion of the dried feces was weighed, ashed for analysis, dissolved in acid and made up to 100 cc. Triplicate 100 cc. specimens of the pooled formulas were dried and ashed for analysis, dissolved in acid and diluted to the original volume. The ashing was done in a muffle furnace at red heat.

A summary of the intake, output, balance, retention and gain in weight for the three day periods are given in table 2. Averages for the entire period are shown in figure 1.

8. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for Determining Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63:** 461, 1925.

9. Youngberg, G.: Phosphorus Metabolism: III. On the Determination of Phosphorus in Urine, J. Lab. & Clin. Med. **17:**1145, 1932.

TABLE 2.—*Summary of Intake, Output and Balance per Kilogram of Body Weight per Three Day Period* *

	Calcium						Phosphorus						
		Output						Output					Body Weight per Kilogram
	Intake	Urine	Feces	Total	Balance	Retention, per Cent	Intake	Urine	Feces	Total	Balance	Retention, per Cent	
Whole boiled cow's milk	113	5.5	53.7	59.2	54	47.8	96.9	45.6	13.8	59.4	37.5	38.7	4.525
	118	5.1	49.3	54.4	64	54.2	99.0	42.3	13.9	56.2	42.8	43.3	4.658
	103	4.5	78.8	83.3	20	19.4	90.3	49.7	24.5	74.2	16.1	17.9	4.633
	104	5.4	61.8	67.2	37	35.6	89.1	40.1	17.6	57.7	31.4	35.3	4.528
Average.....	110	5.1	60.9	66.0	44	39.2	93.8	44.4	17.4	61.9	32.0	33.8	4.586
Liquid milk base exchange treated	87.6	5.0	46.8	51.8	36	41.1	66.0	36.8	11.5	48.3	17.7	26.8	4.688
	93.3	3.6	37.1	40.7	53	56.7	79.6	31.7	11.3	43.0	36.6	46.0	4.662
	92.3	3.0	43.4	46.4	49	53.1	86.5	37.9	10.3	48.2	38.3	44.0	4.688
	92.8	1.1	29.2	30.3	64	68.9	75.0	26.3	5.4	31.7	43.3	57.7	4.793
Average.....	91.5	3.2	39.1	42.3	50	54.9	76.8	33.2	9.6	47.8	34.0	43.7	4.708
Whole boiled cow's milk modified by citric acid	117	2.0	61.3	63.3	54	46.1	101.0	50.0	6.4	56.4	44.6	44.2	4.768
	109	2.1	53.6	55.7	53	48.6	81.0	50.6	5.4	56.0	25.0	30.9	4.798
	114	5.5	73.2	78.7	35	30.7	91.8	70.8	6.3	77.1	14.7	16.0	4.890
	105	3.0	56.6	58.6	46	43.8	86.2	70.0	5.4	75.4	10.8	12.5	4.945
Average.....	111	3.2	61.2	64.3	47	42.3	90.0	60.4	5.9	66.2	23.8	25.9	4.850
Powdered milk base exchange treated	83.5	4.5	46.5	51.0	32	38.3	74.2	41.5	9.0	50.5	23.7	32.0	5.180
	89.6	5.5	58.2	63.7	26	29.0	73.1	43.1	10.7	53.8	19.3	26.4	5.243
Average.....	87.5	5.0	52.3	57.3	29	33.6	73.6	42.3	9.9	52.1	21.5	29.2	5.211
Whole boiled cow's milk	114	5.0	71.4	76.4	38	33.3	89.1	48.4	17.2	65.6	23.5	26.4	5.313
	117	5.4	87.2	92.6	24	20.5	95.9	55.6	22.0	77.6	18.3	19.1	5.385
	112	4.3	92.5	96.8	15	13.4	93.8	42.3	21.5	63.8	30.0	32.0	5.452
	113	4.7	69.0	73.7	39	34.5	98.2	54.5	15.8	70.3	27.9	28.4	5.548
Average.....	114	4.8	80.0	84.9	29	25.4	94.2	50.2	19.1	69.3	24.9	26.5	5.424

* Values are given in milligrams.

RESULTS OF THE METABOLISM STUDY

1. *Control Period.*—The infant was in a positive calcium and phosphorus balance during the two twelve day control periods during which 100 cc. of whole boiled cow's milk per kilogram of body weight was fed. The first control period showed a better balance and percentage of retention than the final control period. This was probably due to the fact that the infant was fed optimum quantities of milk prior to the start of the investigation, while throughout the experimental study, including the last control period, covering a total of fifty-eight days, the infant had been receiving minimum feedings. If, however, in the first

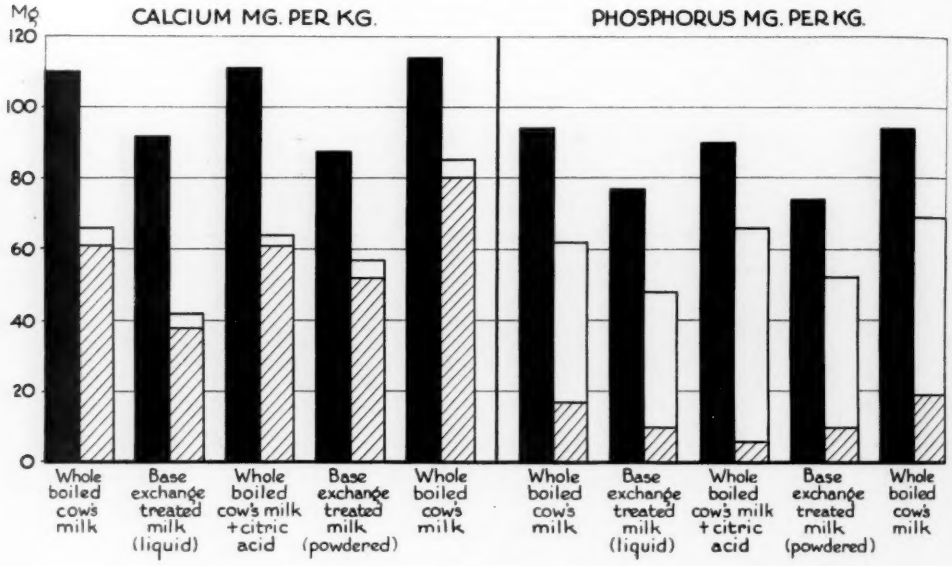

Chart 1.—Average calcium and phosphorus values for the twelve day periods. The solid block indicates intake, the cross-hatched block, feces and the open block, urine.

control period, for the purpose of comparison, six days are allowed for adjustment to the new formula and the values of the last six days of this period are then averaged the values correspond with those of the final control period.

2. *Effect of the Treatment of Milk by Base Exchange.*—The results show that in spite of the lowered calcium and phosphorus content of milk treated by base exchange the infant was in a positive calcium and phosphorus balance during the entire period of feeding. The absolute retention and percentage of retention of calcium and phosphorus were greater when the infant was fed milk treated by the process of base

exchange than when it received untreated boiled cow's milk. The absolute amount of calcium and phosphorus retained per kilogram of body weight was not, however, strikingly increased. This is explained by the fact that the absolute quantities of these salts are lower in the formulas containing milk treated by the process of base exchange. The quantities of these salts present, however, were utilized more efficiently.

3. *Effect of Acidification.*—Whole boiled cow's milk acidified with citric acid to the iso-electric point of the casein (p_H 4.6) caused a better retention of calcium and phosphorus than the control formula consisting of untreated boiled cow's milk. The percentage of retention and total balance of calcium and phosphorus during the period of feeding with acidified milk were lower, however, than when the infant was receiving milk treated by the process of base exchange.

COMMENT ON RESULTS

There are three possible explanations of the increased absolute retention and percentage of retention of calcium and phosphorus with the use of milk treated by base exchange: the curd, the state of the calcium in the milk and the reaction of the ash. The first two factors would be more concerned with absorption and the last more specifically concerned with retention.

Curd.—Brennemann [1] showed that raw cow's milk coagulates in large firm masses in the stomach, that these coagula become larger for about two hours by agglutination and increasingly harder by contraction and that digestion occurs only at the periphery. This also occurs with boiled and diluted milks, except that the changes are less marked. Under these conditions all the calcium and phosphorus may not become available for absorption. With the use of acid, evaporated and dried milks there is practically no formation of curd in the stomach. Milk treated by the process of base exchange, whether liquid or powdered, does not form a visible curd with rennin. When, however, equal quantities of powdered milk treated by base exchange were substituted for the liquid form in the metabolism study there was a lower percentage of retention of calcium and phosphorus. This seems to indicate that something other than the size of the curd is a factor in the differences in the retention of calcium and phosphorus.

State of the Calcium in the Milk.—It has long been known that the calcium in milk exists in two forms, one soluble and one insoluble. Early investigators,[10] using filtration through clay cells, gave values for

10. Duclaux, E.: On the Constitution of Milk, Compt. rend. Acad. d. sc. **98**:438, 1884. Söldner, F.: The Salts of Milk and Their Relation to the Behavior of Casein, Landwirtschaftl. Versuchs-stat. **35**:354, 1888. Ott de Vries, J. J., and Bockhour, F. W. J.: A Contribution to the Knowledge of Rennet Coagulation, ibid. **55**:221, 1901.

the soluble portion of cow's milk from 24 to 47 per cent. Rona and Michaelis,[11] in 1909, using a method of dialysis found from 40 to 50 per cent of the calcium dialyzable. Later workers [12] reported varying results for soluble calcium in cow's milk. Depending on the experimental conditions, values from 18 to 50 per cent have been reported.

Grosser,[12a] who investigated human milk as well as cow's milk, found 44.8 per cent of the calcium of human milk ultrafiltrable. Bosworth,[12j] using the technic described by Van Slyke and Bosworth,[12c] found a value of 60.45 per cent for human milk. Budde,[13] studying the ultrafiltrable calcium and phosphorus in cow's milk from the point of view of infant feeding, found from 20 to 30 per cent of the calcium of skimmed milk and from 65 to 75 per cent of the calcium of human milk ultrafiltrable. The most recent study is that of Hess and Benjamin,[14] in which they determined the ultrafiltrable and the adsorbable calcium and phosphorus in cow's and human milk. They reported an average of 30 per cent ultrafiltrable calcium in cow's milk and 66 per cent in human milk.

In order to evaluate the part the state of calcium played in the results of our metabolism studies, we undertook to compare the ultrafiltrable calcium of milk treated by base exchange with untreated cow's milk, human milk and some of the acidified milks used in infant feeding. Owing to the fact that cow's milk represents a complex and not well

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11. Rona, P., and Michaelis, L.: On the State of Calcium in Milk, Biochem. Ztschr. **21**:114, 1909.

12. (*a*) Grosser, P.: On Influence of Heating on Physical-Chemical Properties of Human Milk, Cow's Milk and Buttermilk, Biochem. Ztschr. **48**:427, 1913. (*b*) Rupp, P.: The Chemical Changes Produced in Cow's Milk by Pasteurization, United States Department of Agriculture, Bureau of Animal Industry Bull. 166, 1913. (*c*) Van Slyke, L. L., and Bosworth, A. W.: Chemical Changes in the Souring of Milk, J. Biol. Chem. **24**:191, 1916. (*d*) Gyorgy, P.: The Partition of Calcium and Inorganic Phosphorus in Milk, Biochem. Ztschr. **142**:1, 1923. (*e*) Wha, C.: Contribution on the State of Calcium, Sodium, Chlorine and Phosphorus in Milk and the Technic of Ultrafiltration, ibid. **144**:278, 1924. (*f*) Bell, R. W.: The Effect of Heat on the Solubility of the Calcium and Phosphorus Compounds in Milk, J. Biol. Chem. **64**:391, 1923. (*g*) Maltick, E. C. V., and Hallett, H. S.: The Effect of Heat on Milk: A. Coagulability by Rennet; B. On the Nitrogen, Phosphorus and Calcium Content, J. Agric. Sc. **19**:452, 1929. (*h*) Rossi, A.: Distribution of Electrolytes in Milk and in the Ultrafiltrate, Boll. d. Soc. ital. biol. sper. **5**:475, 1930. (*i*) Rossi, A.: Distribution of Electrolytes in Milk and in the Dialysate, ibid. **5**:1060, 1930. (*j*) Bosworth, A. W.: Human Milk, J. Biol. Chem. **20**:707, 1915.

13. Budde, O.: The Influence of Digestion on the Solubility of Calcium and Phosphorus in Milk, Monatschr. f. Kinderh. **47**:511, 1930.

14. Hess, A. F., and Benjamin, H. R.: Comparative Analysis of Forms of Calcium and Inorganic Phosphorus in Human and Cow's Milk, Proc. Soc. Exper. Biol. & Med. **30**:1358, 1933.

understood physicochemical system, this investigation was made on the formulas as fed to the infant. Such a procedure would take into account any effect on the state of the calcium due to the dilution with tap water or the addition of lactose. The formulas were all subjected to the same procedure, and the extent of our claim is that they are comparable under the experimental conditions. The formulas studied are listed in table 3.

The comparatively simple apparatus used in this study consisted of an alundum filter cone,[1] 3 inches (7.62 cm.) in diameter, impregnated with a collodion membrane. The alundum cone was placed inside a heavy glass funnel with a rubber gasket between. The funnel was placed in a 250 cc. filter flask, which was connected through a manometer to a suction pump. The specimens were collected in graduated tubes placed directly under the stem of the funnel (15 cc. graduated centrifuge tubes were used).

The method of preparing the cone was essentially the same as that described by Seibert [15] for the ultrafiltration of tuberculin. A 9 per cent solution of collodion in glacial acetic acid was prepared. The moist filter cone was filled with the

TABLE 3.—*Formulas Studied*

Milk	Boiled Tap Water, Cc.	Lactose, Gm.	Acidification
Boiled whole cow's, 100 cc.	75	8	.....
Boiled base exchange treated, 100 cc.	75	8	.....
Powdered base exchange treated, 13.5 Gm.	175	8	.....
Klim, 13.5 Gm.	175	8	.....
Boiled whole cow's, 100 cc.	75	8	Orange juice, 6 cc.
Boiled whole cow's, 100 cc.	75	8	Lemon juice, 2.1 cc.
Boiled whole cow's, 80 cc.	75	8	Tenth-normal hydrochloric acid, 20 cc.
Boiled whole cow's, 100 cc.	75	8	Citric acid, 0.6 Gm.
Boiled whole cow's, 100 cc.	75	8	Lactic acid, U.S.P., 0.8 cc.
Human, 100 cc.	..	..	.....

collodion solution, and suction was continued for one and a half minutes. The cone was then removed and drained until most of the collodion had run off. It was immersed in lukewarm water and washed with distilled water until acid-free. A suction of from 64 to 68 cm. of mercury was used in preparing the cone and for the specimens. When not in use, the cone was kept in water containing a few drops of toluene.

The procedure for running the samples was as follows: The cone was rinsed with distilled water and placed in the funnel, and suction was applied until drops of water no longer formed in the tip. Sixty cubic centimeters of the specimen to be filtered was placed in the cone. The first 0.5 cc. which came through was discarded. The graduated tube was placed under the funnel and suction applied for two hours. The ultrafiltrate was analyzed for calcium, the modification of the Kramer-Tisdall method suggested by Tweedy and Koch [16] being used. It was found

15. Seibert, F. B.: The Chemical Composition of the Active Principle of Tuberculin: XI. An Improved and Simplified Method for Making a Standard Undenatured Tuberculin of Any Desired Strength and a Method of Chemical Assay, J. Biol. Chem. **78**:345, 1928.

16. Tweedy, W. R., and Koch, F. C.: A Suggested Modification of the Kramer-Tisdall Method for the Microchemical Estimation of Ionizable Calcium in Blood Plasma, J. Lab. & Clin. Med. **14**:747, 1928-1929.

necessary to make the portions of the ultrafiltrate used for the analysis for calcium slightly acid with hydrochloric acid and place them in boiling water for a few minutes before adding the ammonium oxalate in order to render the calcium oxalate precipitate coarsely crystalline enough to centrifugate down readily. Duplicate 50 cc. portions of the original specimen were dried, ashed, dissolved in 10 cc. of acid (concenerated hydrochloric acid 1 part and water 3 parts) and diluted to the original volume. Two cubic centimeters of this ash solution was precipitated with 2 cc. of saturated ammonium oxalate, and washed in the same manner as the ultrafiltrates. The precipitate was dissolved in 2 cc. of tenth-normal sulphuric acid and titrated with five hundredths-normal potassium permanganate. The ultrafiltrate from the most acid specimens (p_H 4.4), in which practically all the calcium appeared in the ultrafiltrate, were treated in the same manner as the originals.

The p_H of the original specimen was determined colorimetrically. We are fully aware that the colorimetric method for p_H is not well adapted for milk, but owing to the small volumes of the ultrafiltrate it was considered to be more consistent to use this method for both the original solution and the ultrafiltrate. This method was used throughout, and the conclusions are based on the relative differences observed.[17] The p_H of the ultrafiltrate was determined immediately by the colorimetric method.

The calcium was also precipitated immediately, allowed to stand overnight and determined the next day. Owing to the fact that the lactose present in the ultrafiltrate may ferment and interfere with the determination, the samples were kept in the icebox if they could not be determined within twenty-four hours. Determinations were made in duplicate or when possible in triplicate on 2 cc. portions of the ultrafiltrates.

After the filtration was completed, the cone was washed with warm tap water, then in distilled water. The following solutions in the order named were run through the filter: 70 cc. of tenth-normal hydrochloric acid, 70 cc. of distilled water and 70 cc. of dilute solution of sodium hydroxide (0.1 per cent). The filter was washed with distilled water until the p_H of the water coming through the filter was the same as that of the water put in. The hydrochloric acid served to remove any calcium retained by the filter. The alkali treatment not only neutralized the acid, but also dissolved the protein adsorbed by the filter. The complete filtration was run at least in duplicate on all the formulas studied. The porosity of the filter was standardized and tested after every three or four filtrations by a determination on the specimen used as control (diluted whole boiled cow's milk and lactose). A maximum variation of 0.05 mg. of calcium per cubic centimeter in the ultrafiltrate was allowed. Twenty filtrations of the control specimen done over a period of eight months with five different membranes lay within the range indicated. The filters were all tested and found to be impermeable to protein.

Owing to the fact that there was a marked difference in the rapidity of filtration, all specimens were filtered for the same period of time to make any effect of evaporation constant throughout the series.

The results were recorded as the percentage of the original calcium appearing in the ultrafiltrate, thus putting formulas which contain varying amounts of calcium on the same basis. The results recorded in table 4 represent the averages. The maximum and minimum in each case came within the limits given for the control formula.

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17. A potentiometric determination of the p_H of the control formula gave a value 0.55 p_H unit higher than the colorimetric value.

Our results on cow's milk can be only generally compared with those of other authors, since in our investigation formulas rather than undiluted milk were used. The average value of 22.2 per cent of ultrafiltrable calcium in the control formula is in reasonable agreement with the values reported for cow's milk by other authors. Our value for the percentage of ultrafiltrable calcium in human milk is quantitatively in better agreement with Grosser [12a] than with the other investigators. Our results are entirely in agreement with the conclusion of all of the workers, that the diffusible calcium makes up a larger percentage of the total calcium of human milk than it does of cow's milk. Owing to the fact that for comparative purposes arbitrary factors were used (dilution and time of filtration), too close a comparison cannot be made.

TABLE 4.—*Percentage of Original Calcium in Ultrafiltrate*

Formula		Original Sample		Ultrafiltrate		
		p_H	Mg. per Cc.	p_H	Mg. per Cc.	Per Cent
Control	Average	6.0	0.72	6.5	0.16	22.2
	Number	(20)	(20)	...	(20)	(20)
	Maximum	(6.0)	(0.76)	6.6	(0.18)	(25.6)
	Minimum	(6.0)	(0.69)	6.3	(0.14)	(18.9)
Human*		6.6	0.28	7.2	0.11	38.0
Base exchange treated liquid		6.0	0.58	6.4	0.24	41.4
Base exchange treated powdered		6.0	0.59	6.4	0.17	28.8
Klim		6.0	0.72	6.4	0.10	14.6
Orange juice		5.6	0.69	6.1	0.22	32.0
Lemon juice		5.4	0.73	5.8	0.30	40.7
Hydrochloric acid		5.4	0.61	5.4	0.26	42.7
Lactic acid		4.4	0.73	4.4	0.70	96.6
Citric acid		4.4	0.72	4.4	0.71	98.5

* A pooled sample was used for this test.

The formula containing milk treated by base exchange (p_H 6) showed by our procedure 41.4 per cent ultrafiltrable calcium, approximately twice as much as the formula with whole boiled cow's milk (p_H 6). The amount of ultrafiltrable calcium in the formulas treated by base exchange (p_H 6) is comparable to our average determinations of 38.9 per cent for human milk (p_H 6.6) and some of the results obtained with the ultrafiltration of milks acidified to a p_H of 5.4.

The greater amount of ultrafiltrable calcium in the milk treated by base exchange is possibly dependent on the treatment of the milk with citric acid prior to the treatment by base exchange. Since milk which has been treated by this process will not curdle with the addition of rennin, and since this milk contains more ultrafiltrable calcium than does untreated cow's milk, we can only infer that the ultrafiltrable calcium in the milk treated by base exchange is in a combination in which the ionization of calcium is depressed.

A number of investigators, Grosser,[12a] Van Slyke and Bosworth,[12c] Gyorgy,[12d] Asal-Falk [18] and Wha,[12e] have shown that an increase in the acidity of milk either from the addition of acid or by natural souring increases the ultrafiltrable calcium. When milk is acidified to the iso-electric point of the casein, p_H 4.6, practically all the calcium is found in soluble form. Gyorgy [12d] found that the whey from milk curdled by rennin with no alteration of p_H showed no increase in the content of ultrafiltrable calcium. This observation was later confirmed by Budde.[13]

In this study the ultrafiltrable calcium of formulas of whole boiled cow's milk was found to vary directly with the hydrogen ion concentration. A p_H of about 5.4 renders approximately 40 per cent of the calcium ultrafiltrable, while lowering it still further, to from p_H 4.6 to p_H 4.4, rendered practically all the calcium ultrafiltrable.

Powdered milks (klim and powdered whole milk treated by the process of base exchange) when reliquefied gave slightly but consistently less ultrafiltrable calcium than the corresponding liquid milks. This decrease in ultrafiltrable calcium was not due to the lack of solubility of powdered milks in water, as even when the formulas were allowed to stand twenty-four hours they showed no increase of calcium in the ultrafiltrate. The powdered whole milk treated by base exchange gave quantitatively and proportionately more ultrafiltrable calcium than did powdered whole milk untreated (klim). The lower values of ultrafiltrable calcium in powdered milks may be due to the adsorption of calcium by the casein in the heat processing, as was observed by Ballowitz,[19] or to the disturbance of the mechanism (supersaturation or salt complex) which keeps the excess calcium in solution.

In the application of these data to our work on metabolism we find that we are still concerned with some other factor. The percentage of ultrafiltrable calcium (98.5 per cent) found in the formula containing whole boiled cow's milk to which citric acid was added to a p_H of 4.4 showed that the increase in ultrafiltrable calcium alone was not the determining factor in obtaining an increased retention. Although in acidifying the milk to the iso-electric point of casein practically all the calcium was rendered ultrafiltrable, less calcium was retained in the metabolism study than when liquid milk treated by base exchange was fed (fig. 2). The fact that acidified milk also has a fine curd indicates that some factor other than the size of the curd and the ultrafiltrable calcium must be operative in explaining the differences in the retention of calcium of the milks studied.

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18. Asal-Falk, B.: Contribution to Dietetic Casein Therapy, Jahrb. f. Kinderh. **100**:61, 1923.

19. Ballowitz, K.: Adsorption of Calcium by the Casein in Milk, Biochem. Ztschr. **256**:64, 1932.

Reaction of the Ash.—There are several possible explanations of why increasing the amount of ultrafiltrable calcium in acidified milk did not result in better retention. One is that there may be optimum ingestion of soluble calcium for retention, the excess being excreted regardless of its form. Another possibility is that acidification of milk, even with an organic acid, may interfere sufficiently with the acid base balance to prevent maximum retention. With the present information neither of these factors can be definitely evaluated.

The amount of total fixed base, however, has been shown to be an important factor influencing the degree of retention of calcium. Experimentally, Hamilton and Schwartz [20] were able to prevent rickets com-

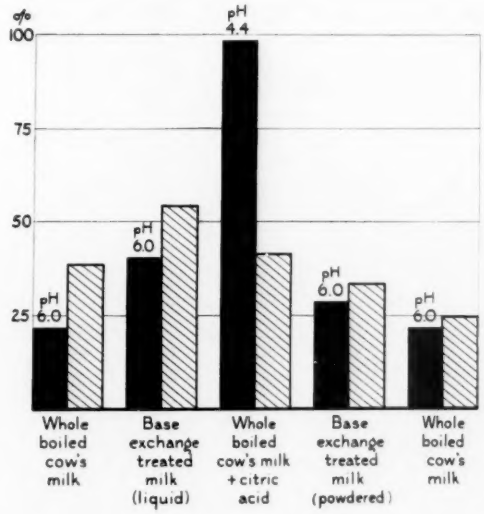

Chart 2.—Comparison of the percentage of ultrafiltrable calcium in the formula with the percentage of retention of calcium. The average is given for the twelve day periods, with the solid block showing the percentage of ultrafiltrable calcium and the cross-hatched block showing the percentage of retention of calcium.

pletely on a rickets-producing diet in animals by the addition of acid sodium tartrate to the diet, thus causing intestinal acidity and metabolic alkalinity. Rickets was produced on a nonrickets-producing diet by the addition of ammonium chloride and ammonium carbonate, thus causing intestinal alkalinity and metabolic acidity. In the application of these experimental data to infant feeding it may be surmised that feeding milk with a small, flocculent curd, containing a good proportion of diffusible calcium, to an infant with a normal p_H of the gastro-intestinal

20. Hamilton, B. K., and Schwartz, C.: Rôle of Acidosis in the Etiology of Rickets, Tr. Am. Pediat. Soc. **55**:47, 1933.

tract may favor absorption. Differences in retention might occur, however, depending on the reaction of the ash of the ingested milk. Milk with a larger amount of fixed base favors metabolic alkalinity. It is therefore of interest to compare the ash of human milk and of cow's milk to see if any correlation exists between these data and the results of our metabolism study.

Table 5 shows that the alkalinity of the ash of the milk treated by base exchange is higher than that of whole cow's milk and is in excellent agreement with the alkalinity of the ash of human milk. A comparison of the composition of the ash of the milks (table 6) shows the increase

TABLE 5.—*Comparison of the Alkalinity of the Ash*

	Ash, per Cent	Alkalinity, Cc. Tenth-Normal Sodium Hydroxide per Gm. Milk	Alkalinity, Cc. Tenth-Normal Sodium Hydroxide per Gm. Ash
Cow's milk*	0.72	0.1547	21.5
Human milk*	0.294	0.1513	51.6
Base exchange	0.63	0.33	52.4

* Data from J. H. Kastle (Am. J. Physiol. **22**: 297, 1908).

TABLE 6.—*Comparison of the Inorganic Constituents of the Ash of Milk* *

	Calcium Oxide	Magnesium Oxide	Sodium Oxide	Potassium Oxide	Phosphorus Pentoxide	Chlorine
Human milk†	0.0458	0.0074	0.0132	0.0609	0.0345	0.0358
Cow's milk‡	0.172	0.02	0.0465	0.1885	0.2437	0.082
Milk treated by base exchange	0.140	0.0243	0.1001	0.1451	0.1994	0.0861

* Values are expressed as grams per hundred cubic centimeters.
† Data from Holt, L. E.; Courtney, A. M., and Fales, H. L.: (A chemical Study of Woman's Milk, Especially Its Inorganic Constituents, Am. J. Dis. Child. **10**: 229 [Oct.] 1915).
‡ Data from Langstein, L., and Meyer, L. F.: Säuglingsernährung und Säuglingsstoffwechsel (Wiesbaden, J. F. Bergmann, 1914, p. 22).

to be due largely to an increase in sodium. This increase in the total fixed base may be the factor involved in the better retention of calcium on milk treated by base exchange than on untreated cow's milk, plain or acidified. Practically, we should not expect these finer changes in the acid base balance to become evident clinically in the feeding of normal infants so long as optimum quantities of milk were fed. It has been established beyond question that the relative utilization of calcium and phosphorus is more complete when human milk is fed than when the infant receives cow's milk. The significance of this fact is obscured clinically when it is noted that the actual amount of calcium and phosphorus retained is higher with cow's milk than with human milk. Even though the utilization is less efficient, the amounts of these salts fed with the use of cow's milk is quantitatively greater, and the difference

in utilization is not observed. In discussing the comparative utilization of calcium of human and cow's milk, Hamilton and Moriarity [21] pointed out that the excess of intake of calcium with cow's milk may obscure the fundamental laws of calcium metabolism.

SUMMARY

1. Whole cow's milk treated by the process of base exchange will keep a normal, growing infant in a positive calcium and phosphorus balance on 100 cc. of milk per kilogram of body weight a day.

2. While there is a reduction in the amount of calcium and phosphorus in milk treated by base exchange the results in the metabolism study indicate that the utilization of these elements is more efficient.

3. The possible mechanism by which more efficient utilization takes place is attributed to three factors: (*a*) the size of the curd; (*b*) the state of the calcium, and (*c*) the reaction of the ash.

4. After evaluating the results obtained from experiments in ultrafiltration and the metabolism study it appears that it is necessary to influence favorably all three factors to obtain a maximum retention of calcium and phosphorus on minimum feedings of milk.

In the treatment of cow's milk by the process of base exchange the curd is modified, the amount of ultrafiltrable calcium is increased and the reaction of the ash is changed so that a greater amount of fixed base is present. These changes appear to be reflected in a better percentage of retention of calcium and phosphorus when milk treated by the process of base exchange is given a normal infant.

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21. Hamilton, B., and Moriarity, M.: Factors Influencing the Excretion of Calcium, Am. J. Dis. Child. **36**:450 (Sept.) 1928.

Case Reports

CARDIAC HYPERTROPHY IN INFANCY

ASSOCIATED WITH THICKENED ENDOCARDIUM AND COARCTATION OF THE AORTA

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A 10 month old infant, who until the day of death had been in perfect health, was recently examined post mortem at the Beth Israel Hospital. There was a markedly hypertrophied and dilated heart, showing fibrous thickening of the left ventricular parietal endocardium without involvement of the valves. In addition, there were narrowing of the descending branch of the left coronary artery and a slight degree of coarctation of the aorta of the infantile type.

REPORT OF CASE

The patient was a 10 month old infant, a first child. The mother was 42 years old when the baby was born; the father, about 45 years old, had always been sickly and had been suspected of having tuberculosis. The pregnancy ran a normal course and the delivery was easy. The child was well until the day of admission, no history of previous infections being obtained.

On the day of onset of the illness the mother had the child at the beach all morning. In the afternoon the baby became ill with fever and malaise, and a physician was called. He found a slightly increased heart rate, a slight rise in temperature and a few "mucous râles" in the lungs. No murmurs were heard. He prescribed medication, but several hours later was again called by the family. At this examination the lungs were filled with râles, and the child was cyanotic and evidently moribund. Immediate hospitalization was advised.

Physical examination on admission revealed a moribund child showing marked cyanosis of the face and extremities, the latter being cold. The eyeballs were rolled upward. Percussion revealed dulness over the entire right and left lung fields. Moist crackling râles were heard throughout both lungs. The heart sounds were very distant. Rectal temperature was 100.4 F. Caffeine sodium benzoate, 0.4 Gm., was given intramuscularly about fifteen minutes after admission, but the patient died five minutes later.

Autopsy (Dr. H. L. Cabitt).—The autopsy, performed nine and one-half hours post mortem, revealed a well developed and fairly well nourished white female infant, showing slight cyanosis of the nail beds. The posterior fontanel was closed, and the anterior fontanel was almost closed. The thymus was not enlarged. It was brownish red and rather firm. It overlay only the great vessels in the superior mediastinum, and was not overlapped by the lungs. Section revealed a

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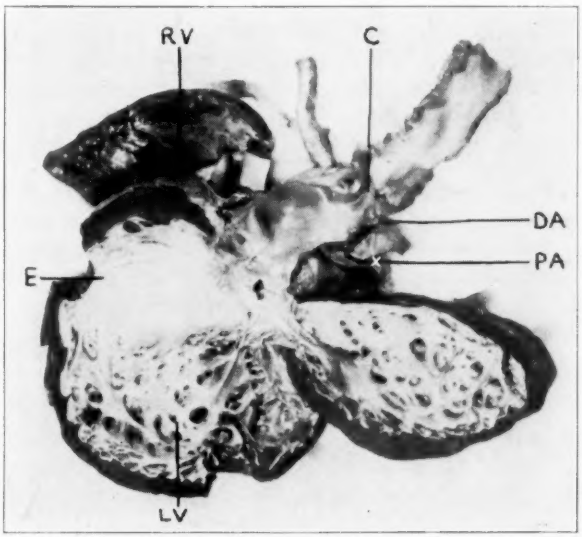
homogeneous, opaque, yellowish-brown cut surface. Both pleural cavities contained a small amount of light yellow, clear fluid.

The heart weighed 150 Gm. (The average weight of the heart at the age of 10 months, according to Bovaird and Nicoll,[1] is 34.2 Gm. Vierordt[2] gave the average weight of the hearts of female infants of from 10 to 11 months as 33.3 Gm.) It lay in its usual position, and was greatly dilated and hypertrophied. The entire endocardium of the left ventricle, grayish-white and considerably thickened, and giving evidence of fibrosis, varied from 0.3 to 0.4 cm. in thickness. The overlying myocardium, having an average thickness of 1.4 cm., was brownish and showed no fibrosis macroscopically. The papillary muscles were not markedly hypertrophied and showed no endocardial thickening. The leaflets of the mitral valve were free and delicate, showing no trace of thickening or fusion. The tri-



Hypertrophy and dilatation of the left ventricle (*LV*), showing the white, opaque and thickened endocardium of the left ventricle, (*E*), in marked contrast to the glistening, translucent endocardium of the right ventricle (*RV*). The obliterated ductus arteriosus (*DA*) joins the pulmonary artery and the coarctation area of the aorta (*C*).

cuspid, aortic and pulmonic valves were likewise normal in all respects. The tricuspid ring measured 6.4 cm., the pulmonic ring, 4.2, the mitral ring, 5.8 and the aortic ring, 3.6 cm. The thickness of the right ventricle was 0.7 cm. The foramen ovale was closed, and there was no patency of the interventricular septum. The endocardium of both auricles and the right ventricle was smooth, glistening, transparent and light brown. The descending branch of the left coronary artery

1. Bovaird, D., and Nicoll, M.: The Weights of the Viscera in Infancy and Childhood with Special Reference to the Weight of the Thymus Gland, Arch. Pediat. **23**:641, 1906.

2. Vierordt, H.: Daten und Tabellen für Mediziner, ed. 3, Jena, Gustav Fischer, 1906, p. 37.

became markedly narrowed at a point about 1.5 cm. from the origin of the left coronary artery. Distal to this short stenotic area the artery resumed its normal width, which it maintained for the rest of its course. The circumflex branch of the left coronary artery was wide and patent throughout.

There was definite coarctation of the aorta, the location of the narrowed lumen being between the origin of the subclavian artery and the point of insertion of the obliterated ductus arteriosus into the aorta. While the aortic circumference just above the aortic valve was 3.1 cm., its measurement at the coarctation area was 1.5 cm. Distal to this the aorta had its usual caliber.

The right lung weighed 120 Gm. and was normal. The left lung was almost completely atelectatic, weighing 40 Gm.

The peritoneal cavity contained a slight amount of clear, amber fluid. The entire gastro-intestinal tract was markedly congested and edematous. Peyer's patches were very prominent and markedly congested. The liver, spleen and kidneys shared in the congestion. The brain, pancreas, gallbladder, suprarenal glands, bladder and genitalia were normal.

Microscopic examination of the muscle of the heart disclosed intact muscle fibers, showing the striations clearly. Neither the individual muscle fibers nor the nuclei appeared to be increased in size. There was no inflammatory reaction, and slight perivascular fibrosis was present. No Aschoff bodies were seen. The endocardial fibrous tissue was markedly increased in thickness, standing out prominently in sections stained with van Gieson's stain and phosphotungstic acid and hematoxylin. No cellular infiltration was seen in this fibrous connective tissue. Microscospic examination of the thymus showed only severe edema. The histologic observations in the other organs were not remarkable.

REPORTS IN THE LITERATURE

The combination of stenosis of the aorta or of the pulmonary artery with cardiac hypertrophy in infants in the first two months of life was mentioned as early as 1850 by Bednar.[3] Riesenfeld[4] described a case of congenital cardiac failure due to hypertrophy and dilatation of both ventricles, especially of the left, slight stenosis of the isthmus aortae and dilatation of the ascending aorta. Associated with this was the so-called status thymicolymphaticus.

Reports of only eight cases could be found of hypertrophy of the heart in infants associated with a thickening of the parietal endocardium without valvular lesions. Hedinger,[5] in 1904, described a heart weighing 190 Gm. removed from a 14 month old infant. It showed diffuse thickening of the endocardium of the left ventricle, giving the wall a somewhat tendinous appearance, the right ventricle showing a similar appearance in only a few areas. The valves were normal, and there were no associated congenital cardiac defects. Microscopic examination showed

3. Bednar, A.: Die Krankheiten der Neugeborenen und Säuglinge, Vienna, C. Gerold, 1850, pt. 3, p. 160.

4. Riesenfeld, A.: Ueber .primäre Herzhypertrophie im frühen Kindesalter und ihre Beziehung zum Status thymicolymphaticus, Jahrb. f. Kinderh. **86**:419, 1917.

5. Hedinger, E.: Primäre angeborene Herzhypertrophie, Virchows Arch. f. path. Anat. **178**:264, 1904.

a normal myocardium. The last of five cases of cardiac hypertrophy in early childhood reported by Oberndorfer [6] was that of a 14 month old boy who died of poliomyelitis and encephalitis. The heart weighed 136 Gm. The endocardium of the ventricles was thickened. The anterior and posterior walls of the left ventricle showed an almost aneurysmal dilatation, and there was marked flattening of the trabeculae. Here again the valvular apparatus was intact, and there were no congenital cardiac defects. Microscopically, there was enlargement of the muscle cells and their nuclei, some cells appearing to possess two nuclei. Krstulovic [7] described a case strongly suggestive of subacute bacterial endocarditis superimposed on a thickened endocardium. The heart of a 9 month old infant, weighing 100 Gm., showed a normal endocardium in the right ventricle and in both auricles. There was, however, a uniform, diffuse, grayish-white thickening of the endocardium of the left ventricle. Numerous small patches of vegetation covered or lay in the niches between the trabeculae of the anterior wall of the left ventricle just below the aortic valve. These were covered by thrombi, the superficial layers of which showed, microscopically, fibrin nets enmeshing polymorphonuclear leukocytes and larger and smaller accumulations of red blood corpuscles. No bacteria were described. This layer gave way to a band of tissue containing proliferating fibroblasts, and this in turn was surrounded by a layer of vascular granulation tissue containing in its loose meshes numerous lymphocytes and plasma cells. There was a light inflammatory reaction in the neighboring myocardium. In addition, focal nephritis was also demonstrated histologically. Steiner and Bogin [8] described a heart weighing 63 Gm. in a 3 month old boy. The left ventricular endocardium was grayish white and much thickened. The aorta and coronary vessels were normal; the ductus arteriosus and foramen ovale were closed. Microscopic examination of the heart showed edema and moderate hypertrophy of the muscle bundles. No lymphocytic infiltration could be found in any section through the auricles, ventricles, valves and vessels. The thymus was enlarged, weighing about three times the average, and the mesenteric lymph nodes as well as Peyer's patches were markedly enlarged.

In addition to the cases described, in which the endocardial thickening was for the most part uniform and diffuse, a few hearts showing irregular endocardial thickening have been described. Hauser [9] described

6. Oberndorfer: Herzhypertrophien im frühensten Kindesalter, Verhandl. d. Gesellsch. f. Kinderh. **23**:181, 1906.

7. Krstulovic, E.: Zur Frage der idiopathischen Herzhypertrophie, Monatschr. f. Kinderh. **33**:113, 1926.

8. Steiner, M., and Bogin, M.: Idiopathic Cardiac Enlargement Associated with Status Thymicolymphaticus, Am. J. Dis. Child. **39**:1255 (June) 1930.

9. Hauser: Ein Fall von Stenocardia cordis beim Kinde, Deutsche med. Wchnschr. **25**:453, 1899.

a heart showing great thickening of the endocardium of the left ventricle, the thickening being most pronounced just below the aortic valve, where it produced an effective subaortic stenosis. The mitral and aortic valves were uninvolved. A similar, though much less marked, endocardial thickening and ringlike narrowing was present in the right ventricle. Michaud [10] described a heart weighing 155 Gm. removed from a 3 year old child. The endocardium of the left ventricle, particularly that portion toward the conus arteriosus, showed a rather opaque, tendinous thickening. The right ventricular endocardium was likewise, but less extensively, thickened. There was slight thickening of the free edge of the leaflets of the mitral valve; otherwise no valvular defects were seen. Microscopically, hypertrophy of the individual muscle fibers was seen; otherwise no abnormality was observed. Carrington and Krumbhaar [11] described a heart showing a greatly hypertrophied and dilated left ventricle, the endocardium being thickened in the basal portion and on the septum. The left auricle was likewise dilated and hypertrophied and was lined by a uniformly thick and opaque endocardium. Microscopically the individual muscle fibers were enlarged, and there was diffuse interstitial fibrosis in sections from the anterior papillary muscle of the mitral valve and the anterior portion of the septum, this fibrosis being nearer the endocardium than the pericardium. Crawford and Weiss [12] recently described a heart weighing 79 Gm., in a 14 week old infant. The left ventricular endocardium, particularly that overlying the interventricular septum and that beneath the aortic cusps, was grayish and thickened. There were no valvular lesions or congenital defects of the heart. The endocardium of the left auricle seemed slightly thickened. Microscopic examination showed myocardial and endocardial fibrosis.

Interesting particularly from the standpoint of etiology was the bizarre heart described by Winkler.[13] The heart was removed from a 4 week old infant, whose mother had advanced pulmonary tuberculosis and who had acquired gonorrhea during pregnancy. The heart weighed 52 Gm., the enlarged right ventricle constituting the great bulk of this hypertrophy, the left ventricle being a diminutive appendage of the right. The endocardium on the right side of the heart was normal. A tough and tendinous strand of thick tissue stretched from the inter-

10. Michaud, L.: Beitrag zur Kenntnis der kongenitalen idiopathischen Herzhypertrophie, Cor.-Bl. f. schweiz. Aerzte **36**:779, 1906.

11. Carrington, G. L., and Krumbhaar, E. B.: So-Called Idiopathic Cardiac Hypertrophy in Infancy, Am. J. Dis. Child. **27**:449 (May) 1924.

12. Crawford, B. L., and Weiss, E.: Primary Congenital Hypertrophy of the Heart, J. Tech. Methods **12**:182, 1929.

13. Winkler: Endocarditis foetalis, ein Beitrag zur Pathologie des angeborenen Herzfehlers, Verhandl. d. deutsch. path. Gesellsch. **15**:247, 1904.

ventricular septum across the left ventricular cavity to the opposite wall, where it was inserted between the papillary muscles of the mitral valve. The endocardium of the ventricle was markedly thickened, tendinous and glistening, the inner surface of the ventricle being smooth and showing no trace of trabeculation. The aortic valve possessed only two cusps, which showed small grayish-red deposits. The foramen ovale admitted a 2 mm. probe, and the ductus arteriosus for the greater part of its lumen was still patent.

A similar thickening of the parietal endocardium without valvular involvement has been described in adults. Most of these cases were reported before the recognition of the clinicopathologic entity of coronary occlusion and myocardial infarction, with possible subsequent healing. Hence, many of the cases catalogued as chronic parietal endocarditis in adults probably actually represent healed myocardial infarcts. The heart described by Kockel [14] may be a case in point. He described a frosting-like thickening of the parietal endocardium of the left ventricle, with patchy extension of the fibrosis into the myocardium for a depth of from 4 to 5 mm. The age of the patient and the weight of the heart were not given. The first of five hearts described by Bäumler [15] showed irregular thickening of the endocardium and extensive mural thrombosis associated with pulmonary infarction. The left coronary artery was somewhat narrowed at a point about 3 cm. from its origin. The second heart he described showed rigid coronary arteries, and the myocardium, dark brownish-red streaked with small whitish areas in the outer layers, was almost tendinous in appearance in the inner layers. In the third case, however, he described normal vessels in a dilated heart weighing 590 Gm., showing auricular thrombosis, diffuse scarring of the left ventricular endocardium and slight adhesion of the leaflets of the mitral valve. The hearts described by Nauwerck [16] and Bence-Jones [17] likewise apparently showed healed myocardial infarction with endocardial involvement.

COMMENT

One is dealing, then, with a markedly hypertrophied infant's heart, showing diffuse endocardial thickening in the left ventricle and partial occlusion of the descending branch of the left coronary artery associated

14. Kockel: Schmidt's Jahrb. **253**:270, 1897.

15. Bäumler, C.: Das Krankheitsbild der reinen chronischen sog. Wandendokarditis (flächenhafte Endo-Myokardschwiele), Deutsches Arch. f. klin. Med. **103**: 1, 1911.

16. Nauwerck, C.: Ueber Wandendocarditis und ihr Verhältniss zur Lehre von der "spontanen Herzermattung," Deutsches Arch. f. klin. Med. **33**:210, 1883.

17. Bence-Jones: Fibrinous Deposits in the Substance of the Heart, Tr. Path. Soc. London **7**:167, 1856.

with coarctation of the aorta. From the pathologic standpoint the presence of coarctation and endocardial fibrosis immediately excludes this case from the category of "idiopathic" hypertrophy of the heart.[18] Emerson and Green,[19] however, chiefly on clinical grounds, expressed the belief that cases should not be excluded from the classification of idiopathic hypertrophy merely because there is an associated simple defect. They noted the strong clinical resemblance between cases of hypertrophy with, and hypertrophy without, simple defects, and concluded that cases in the latter group are worthy of reporting as a class. In clinical history, observations and course the case reported here differs in no essentials from the bulk of reported cases of idiopathic hypertrophy.[20]

As to the etiology of the cardiac enlargement and the other changes, numerous possibilities offer themselves. The facts of the case certainly do not accord with the hypotheses of status thymicolymphaticus, congenital rhabdomyoma,[21] hyperplasia of the chromaffin system [22] or hypoplasia of the chromaffin system,[10] suggested by others.

The following deserve serious consideration:

1. Developmental Anomalies. The associated coronary narrowing and coarctation of the aorta may represent the result of circulatory disturbances in the fetus.[23] The endocardial fibrosis might conceivably be secondary to the coronary narrowing, but against this are the partial nature of the narrowing of the vessel, the diffuse and uniform distribution of the endocardial fibrosis and the lack of myocardial fibrosis.

2. Mechanical Factors. The coarctation of the aorta by narrowing the proximal vascular bed may have made necessary a compensatory elevation of blood pressure. How far this factor may have been operative is difficult to evaluate, but since the caliber of the aorta at the point of stenosis is only slightly diminished and since there is no evidence of compensatory collateral circulation between the upper and lower parts of the body, it is unlikely that there was any marked elevation of pressure from this cause. It is also conceivable that the thickening of the endocardium as well as the myocardial hypertrophy represents a mechan-

18. Stoloff, E. G.: So-Called Idiopathic Enlargement of the Heart in Infancy and in Childhood, Am. J. Dis. Child. **36**:1204 (Dec.) 1928.

19. Emerson, P. W., and Green, H.: Idiopathic Hypertrophy of the Heart in Infants, Am. Heart J. **4**:116, 1928.

20. Howland, J.: Idiopathic Hypertrophy of the Heart in Young Children, in Contributions to Medical and Biological Research, dedicated to Sir William Osler, New York, Paul B. Hoeber, Inc., 1919, vol. 1, p. 582. Stoloff.[18]

21. Virchow, R.: Berl. klin. Wchnschr. **33**:679, 1896.

22. Wiesel, J.: Zur Pathologie des chromaffinen Systemes, Virchows Arch. f. path. Anat. **176**:103, 1904.

23. Simmonds, M.: Ueber kongenitale primäre Herzhypertrophie, München. med. Wchnschr. **46**:108, 1899.

ical response to an increased load thrown on the heart. This more or less accords with the limitation of the endocardial thickening to the left ventricle without involvement of the parietal endocardium of the other three cardiac chambers and of the entire valvular apparatus. But since hypertension and cardiac hypertrophy in children from so many causes have not been associated with endocardial thickening one may safely dismiss this possibility.

3. Inflammatory Processes. One might hold that the thickening of the endocardium is the end-result of an inflammatory process which existed either in fetal life [24] or during early infancy. Against this is the lack of valvular involvement and the total lack of a trace of inflammatory reaction in the endocardium and myocardium in numerous histologic preparations studied.

4. Toxic Influences. Toxins of maternal origin may diffuse through the placenta, producing deleterious effects on the fetus. This theory was discussed by Fischer.[25]

5. Combination of Factors. The mechanical and inflammatory factors, for example, may have been operative together; that is, there may have been parietal endocarditis which healed to form a thickened fibrous endocardium, while the coarctation of the aorta (itself developmental or inflammatory in origin), by making necessary a higher blood pressure, brought about myocardial hypertrophy.

Mention may perhaps be made of the theoretical possibility that all cases of cardiac hypertrophy with thickened endocardium in infants are not invariably fatal in infancy or childhood and that such cardiac defects seen in adults may have been acquired in infancy or before. By seeing only the fatal cases one perhaps gains a distorted idea of the malignancy of the condition.

SUMMARY

A case of hypertrophy of the heart in a 10 month old infant is described. The heart, weighing 150 Gm., showed no valvular defects, but the endocardium of the left ventricle was uniformly and diffusely thickened and opaque. There was narrowing of the descending branch of the left coronary artery with partial coarctation of the aorta of the infantile type. No inflammatory reaction was seen in the heart.

The literature on the condition is reviewed, and the various etiologic possibilities are discussed.

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24. Farber, S., and Hubbard, J.: Fetal Endomyocarditis: Intrauterine Infection as the Cause of Congenital Cardiac Anomalies, Am. J. M. Sc. **186**:705, 1933. Winkler.[13]

25. Fischer, B.: Ueber fötale Infektionskrankheiten und fötale Endokarditis, Frankfurt. Ztschr. f. Path. **7**:83, 1911.

SITUS INVERSUS IN A DWARF

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There are two points of especial interest in this report. First, this type of dwarfism is rare. Second, the associated situs inversus is of interest when considered in relation to the experimental work on twins in lower animals. I found no report of a like case in the literature.

REPORT OF A CASE

A. V. was first seen at the pediatric clinic of the Northwestern University Medical School in March 1932. He was 9 years old, but his size was that of a 3 year old child. He was small in all dimensions but symmetrically proportioned, a true miniature.

At birth, which was a normal full-term, vertex delivery, he weighed 6 pounds (2,721.5 Gm.). His first year of life was one of uneventful progress on breast feeding and the usual accessory foods started at the proper time. His only illness was measles at 3 years of age. It was the opinion of the parents that his growth had been normal up to 3 years of age. Since that time he had been markedly undersized for his years.

The family history was unimportant. The father, aged 36, and the mother, 29, were well and of average height. A brother of 11 years and a sister of 3 years were normal.

The child weighed 27 pounds (12.2 Kg.); his height was 36 inches (91.4 cm.); the crown-rump length, 21⅝ inches (54.9 cm.) and the circumference of the head, 25¼ inches (64.14 cm.). There was a complete situs inversus of the thoracic and abdominal viscera, verified by roentgenograms. The patient was right-handed and the hair whorl was clockwise. The systolic blood pressure was 84, the diastolic, 42. The physical examination otherwise gave negative results. All laboratory tests including the Wassermann and Kahn tests on the blood, urinalysis, red and white blood cell counts, hemoglobin determination and the Mantoux test gave normal results.

His basal metabolic rate was plus 2 per cent.

The cholesterol content of the blood was 0.195 mg. per hundred cubic centimeters.

A roentgenogram of the skull showed the sella turcica to be normal.

The electrocardiogram showed a deviation of the axis to the right with an inversion of the T and P waves in lead one. The electrocardiographic findings were compatible with the diagnosis of a congenital mirror image with dextrocardia.

The patient's intelligence quotient, based on the Stanford-Binet tests, was 79, which corresponded with the general impression gained by talking with him.

Presented before the Chicago Pediatric Society, April 1933.

From the Department of Pediatrics, Northwestern University.

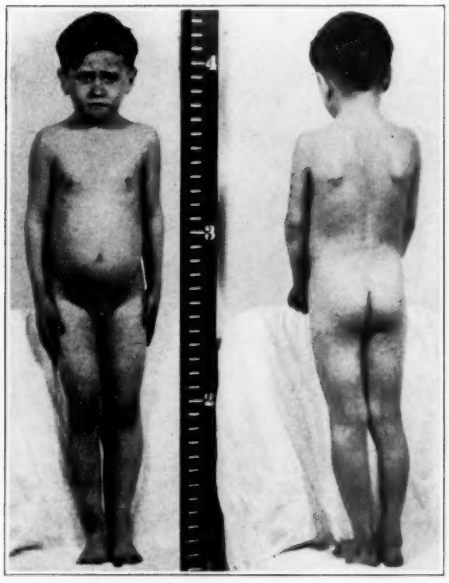

Fig. 1.—Anterior and posterior views of a minature boy of 9 years. Note the symmetry of his dimensions.

Fig. 2.—Roentgenogram showing a complete transposition of the viscera, a mirror-like reversal as compared with the normal.

Fig. 3.—Roentgenogram of a lateral view of the skull, showing a normal sella turcica.

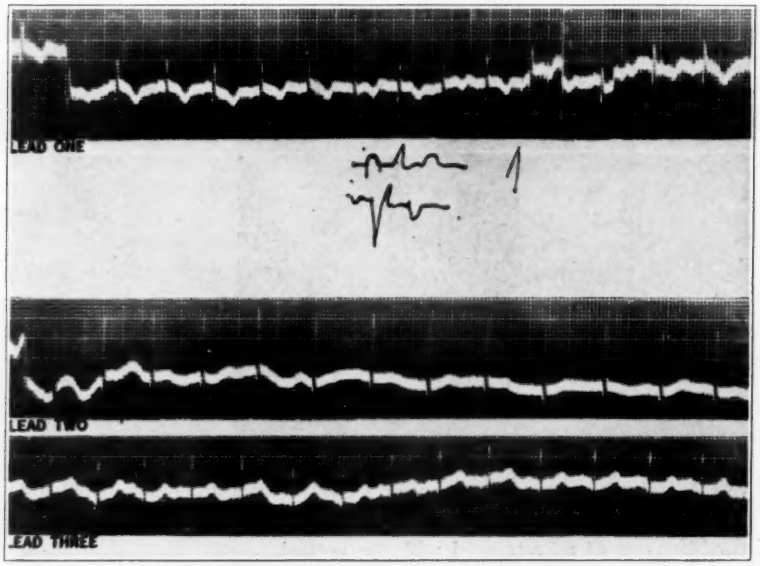

Fig. 4.—Electrocardiogram in a case of situs inversus.

COMMENT

There is nothing in the history or examination of this child to suggest an imbalance of the endocrine glands as the cause of his dwarfism.

His normal proportions, though on a miniature scale, together with the situs inversus, lead one to suspect that he was developmentally one of twins and the mirror image of the other half of the fertilized ovum, and that he possessed only one half the potentiality for growth of the whole zygote. The other half presumably failed to develop after division.

JUVENILE PEMPHIGUS

TREATMENT WITH GERMANIN (BAYER 205); REPORT OF A FATAL CASE

NORMAN TOBIAS, M.D.

ST. LOUIS

REPORT OF A CASE

History.—R. M. G., a white girl, aged 5 years, was admitted to the division of pediatrics of St. Mary's Hospital in February 1932, suffering from an extensive eruption of blisters on the skin, irritability and loss of appetite. She had had measles at 3 years of age and scarlet fever without apparent complications one year before admission. She had been vaccinated successfully when 3 years old. The family history was irrelevant.

Physical Examination.—The child was fairly well nourished and weighed 35 pounds (15,875 Gm.). However, she appeared restless and irritable. The skin was covered with a generalized eruption, the lesions being more pronounced around the mouth, the axillae, the extensor surfaces of the forearms and on the thighs. Some of the bullae were on an erythematous base but most of them appeared to arise from the normal skin. Many of the older lesions were covered with thick, brownish crusts. Nikolsky's sign was present. There were a few lesions on the scalp and the back of the neck. The bullae were flaccid and varied in size from 5 mm. to 1 cm. The general physical examination gave essentially negative results except for the presence of hypertrophic tonsils and adenoids.

Laboratory Examination.—A phytopharmacologic test was reported by Dr. Pels as indicating toxicity. Blood chemistry revealed: nonprotein nitrogen 32 mg.; calcium 8.8 mg.; sugar 100 mg. per hundred cubic centimeters. The blood count gave the following results: red blood cells, 4,390,000; white blood cells, 15,800. Hemoglobin, 74 per cent. The differential count (Schilling) showed: young forms, 1 per cent; stab forms, 5 per cent; segmented forms, 66 per cent; lymphocytes, 25 per cent; monocytes, 3 per cent; eosinophils, 2 per cent. The blood platelets numbered 400,000. The clotting time was three minutes.

Blood cultures made on Feb. 10, 1932, and July 21, 1932, were negative.

Cultures made from the fluid obtained from the blebs contained bacteria in chains and pairs which gave no growth; their injection into the peritoneal cavity of a guinea-pig gave negative results. Cultures taken from the nose yielded gram-positive cocci in groups which produced white colonies on Löffler's culture medium but revealed no Bacillus diphtheriae. Cultures obtained from the throat contained gram-positive cocci in groups, pairs and chains.

All cutaneous tests with the usual foreign proteins gave negative results except for slight reactions in the case of white flour, lemons and oranges.

The urine was at all times free from albumin and sugar. Centrifugated specimens showed a few leukocytes and epithelial cells.

A roentgenogram of the chest showed the lungs to be normal. The cardiac shadow was enlarged to the left.

From the Department of Dermatology of the Pediatric Divison, St. Mary's Hospital and St. Louis University.

Course of the Disease.—The patient entered the hospital on Feb. 3, 1932. Under local treatment the condition improved slightly but no marked progress was made. For several weeks she had a septic temperature and at times gastric distress. In August she was given four injections of Bayer 205 after which the condition of the skin improved 90 per cent and the irregular temperature dropped to normal, and at the end of the last injection only two or three small bullae were left, the lesions on disappearance leaving pigmented areas.

On September 27 a tonsillectomy was performed in the hope that her condition might be improved but new groups of lesions appeared soon after, and on October 30 it was decided to repeat the course of four injections of Bayer 205.

She again improved considerably, but not to the extent noted in the first series. She was permitted, however, to go home on November 16. Five days later she became very irritable and had attacks of vomiting. She was brought to St. Mary's Clinic in a toxic condition which was regarded as serious, and she was removed to St. Mary's Hospital. At this time her temperature was 102 F. The child was found dead fourteen hours after admission, before blood transfusion could be carried out.

Fig. 1.—Appearance of patient one month before beginning treatment with Bayer 205.

Summary of Treatments.—During the first few months of her stay at the hospital, she was given baths of starch and soda, 1 cc. of a blood coagulating preparation every other day and 1 tablet of acetarsone, three times a day. Because of the lack of progress and the septic temperature she was given intramuscular injections of milk, but new lesions continued to appear so that this procedure was discontinued.

After consultation with Dr. Joseph Grindon who verified the diagnosis of pemphigus, the patient was given treatments with hot air and a solution of potassium arsenite. Improvement not being noted, ultraviolet therapy was instituted and viosterol was given daily for thirty days. The latter had to be discontinued because of its ineffectiveness in this case.

In July the patient was given baths of hypertonic saline solution. These were later changed to baths of a potassium permanganate solution because of the foul odor of the lesions. The lesions were swabbed with 1 per cent acriflavine and the child was put on a diet high in vitamins.

On August 15 it was decided, in view of the patient's lack of progress and continued septic temperature, to try Bayer 205 which had been recommended by various German dermatologists for pemphigus. She was given four intravenous injections at four day intervals, the doses ranging from 0.5 to 0.75 Gm. The second series of Bayer 205 treatments were given in October, 0.75 Gm. being used

Fig. 2.—Photograph taken one week after first course of treatments with Bayer 205, and showing the disappearance of most of the bullae. A few crusted lesions and numerous pigmented areas remain.

for each injection. At no time were there any reactions nor did the urine show any evidences of irritation.

Postmortem Examination.—The autopsy was performed by Dr. Collier and Dr. Roberts.

Macroscopic Examination: The heart was about normal in size but was very pale and slightly softer than normal. The coronary arteries showed nothing remarkable. On section the cardiac musculature was seen to be very pale and almost bloodless. The aortic, pulmonary and tricuspid valves showed nothing remarkable. The mitral valve, however, showed many fine, almost transparent vegetations along the line of closure of the leaflets.

The liver was large and extended about 1½ inches (3.8 cm.) below the costal margin in the midclavicular line. It was soft and friable. The surface was reddish purple. The parenchyma was paler than normal and very friable.

The spleen was enlarged to about twice its normal size and was soft, mushy and dark purple. On section the cut surface was very soft and bloody and large amounts of degenerated pulp could be seen.

Both kidneys were slightly larger than normal and pale red. No scars were present on the capsular surfaces but some evidence of fetal lobulation still persisted. On section the cortex and medulla were found to be slightly increased in thickness and all vessels were moderately congested. The capsules stripped without difficulty.

Microscopic Examination: The epicardium showed a moderate thickening due to proliferating young fibrous tissue and an infiltration of lymphocytes and plasma cells. The myocardium showed a moderate atrophy of the muscle fibers and a marked interstitial edema. The endocardium was slightly increased in thickness. The valvular leaflets were thickened and adherent to their outer edges were many tiny thrombi containing a few polymorphonuclear leukocytes and lymphocytes. The coronary vessels showed a nodular thickening of the intima.

The venous sinusoids of the liver were congested, and the cells of the hepatic cords had undergone an extreme atrophy and vacuolar degeneration which was most marked in those about the periphery of the lobules. The central veins were dilated and their walls thickened. The interlobular tissue showed a moderate increase in fibrous tissue, a lymphocytic infiltration, a degeneration of the epithelium of the bile ducts and congestion of the portal vessels.

The splenic corpuscles were hyperplastic and degenerated in their central portions. The splenic pulp was markedly congested and degenerated and was filled with large numbers of pigmented phagocytes, eosinophils and polymorphonuclears. The capsule was thin and appeared stretched.

The glomeruli of the kidneys were markedly congested, but there was no apparent hemorrhage into the glomerular capsules. The endothelial cells of the capillary loops were swollen and vacuolated. The tubular epithelium showed an extreme degree of cloudy swelling and albuminous degeneration, and sloughing into the lumens. No red blood cells were present within the tubules. All blood vessels were markedly congested and in many places capillary hemorrhage had occurred into the interstitial tissue. No polymorphonuclear leukocytes were present anywhere in the sections.

A section taken from one of the encrusted cutaneous lesions, clinically diagnosed as pemphigus, revealed the following pathologic characteristics:

The epidermis showed a moderate hyperkeratosis and acanthosis, and an invagination of the basal cell layer into the dermis. The prickle cell layer in its upper third portion had been separated by an accumulation of serous fluid. This fluid contained many degenerating, desquamated prickle cells, a few lymphocytes and a heterogeneous cellular débris. Overlying the cornified layer was a thick crust of fibrin containing a great number of polymorphonuclear leukocytes. Beneath the epidermis the dermis was moderately thickened and contained a large number of small congested blood vessels. Many of these vessels had ruptured, permitting hemorrhage into the loose tissue of the dermis. In the subcutaneous fatty tissue, all of the tiny capillaries were congested and many lymphocytes,

plasma cells and a few polymorphonuclear leukocytes were infiltrated between the fat cells. A subcutaneous lymph node showed complete loss of architecture owing to the hyperplasia and degeneration of the lymph follicles and the congestion of all the vessels.

Pathologic Diagnosis: The diagnosis was: (1) multiple, encrusted cutaneous lesions, diagnosed clinically as pemphigus; (2) septicemia; acute verrucose endocarditis; acute splenic tumor; acute toxic hepatitis; myocarditis; hemorrhagic Bright's disease; chronic passive congestion of all viscera; (3) generalized vascular intimal proliferation.

TREATMENT

One approaches the subject of therapeusis in pemphigus with a great deal of trepidation. The disease is not only subject to spontaneous remissions with clinical improvement but, since most patients are treated by several therapeutic methods, it is difficult to evaluate the effective agent. Furthermore, it is questionable in a disease in which the etiologic agent is unknown whether so-called cures are not due to the patient's own immunity rather than to any physical or chemical procedure. Most patients die regardless of the form of therapy, some do well with one particular agent while others are made worse, and still another group improve temporarily with any change of therapeutic procedure.

Skepticism in the treatment of pemphigus is further increased by the fact that many dermatologists believe that all patients with true cases of this disease eventually die. Those that survive any therapeutic regimen they regard as having cases of pemphigoid dermatitis and not of true pemphigus. This is the status quo of the problem. In spite of this, Bayer 205 was used in the treatment of my patient for two reasons: first, to attempt clinical improvement and, second, to verify the results of continental investigators.

Before therapy with Bayer 205 was used, the treatment was started with acetarsone, an arsenical preparation, which has been lauded by Oppenheim [1] and others. The use of tryparsamide which Grindon [2] successfully employed in acute and chronic pemphigus was not deemed advisable because of the age of the patient. Unfortunately the transfusions advised by Hollander [3] and the colonic irrigations used successfully by Schamberg [4] were not attempted. Davis and Davis [5] reported

1. Oppenheim, M.: Ueber die Verwendung des Spirozids beim Pemphigus vulgaris chronicus und vegetans nebst Bemerkungen zur Spirozid Therapie, Dermat. Wchnschr. **91**:1855 (Dec. 20) 1930.

2. Grindon, J.: Tryparsamide in Acute Pemphigus, Arch. Dermat. & Syph. **21**:25 (Jan.) 1930.

3. Hollander, L.: Pemphigus; Use of Whole-Blood Transfusion as Aid in Therapy; Preliminary Report, Brit. J. Dermat. **39**:450 (Nov.) 1927.

4. Schamberg, J. F.: Pemphigus: Recovery Following Long-Continued Colonic Irrigations and Arsenic by Mouth, Arch. Dermat. & Syph. **25**:134 (Jan.) 1932.

5. Davis, W. D., and Davis, R. H.: A Contribution to the Treatment of Pemphigus, Arch. Dermat. & Syph. **8**:627 (Nov.) 1923.

cures with a blood coagulating preparation and injections of sodium arsenate in two patients with juvenile postvaccinal pemphigus and one with septic pemphigus. The blood coagulating preparation failed to produce results in my case although it was combined with acetarsone and later with a solution of potassium arsenite.

Bayer 205 originally was introduced by Kleine [6] in 1921 for the treatment of trypanosomiasis in which it has been remarkably successful. Homann [7] and others have used it in multiple sclerosis with varying results. Veiel [8] in 1931 first suggested its use in pemphigus. He reported three cures among four patients and requested further experimentation with the drug.

Bayer 205 is a carbamide of a complex salt of trisulpho acid. It has an action similar to sodium citrate on the coagulability of the blood. In large doses it may irritate the kidneys. In proper doses it may aggravate an existing nephritis. No untoward effects have been reported in its use with the exception of dermatitis in MacLean's case of trypanosomiasis [9] and erythema in the cases of pemphigus reported by Gieseln [10] and Veiel.[8]

The drug is a white powder, slowly soluble in water. Intravenous injection is preferable, the dose being carefully dissolved in 10 cc. of sterile distilled water. The first dose is 0.3 Gm.; it is increased to 0.75 Gm. and then to 1 Gm. and the dose given every other day. It is advisable not to exceed a total of five doses to a course, which may be repeated in from four to seven days if deemed necessary and if renal function is normal.

As a rule the injections are well borne, although occasionally a chill or a rise in temperature may follow. The urine must be examined after each injection. The presence of a moderate amount of albumin or casts or an increase in the nonprotein nitrogen content of the blood demands a smaller dosage, a longer interval between doses and careful observation of the patient. Similar renal tests must be carried out after the course of injections is completed.

More than eighteen cures and four deaths in patients treated with Bayer 205 have been reported in the literature. The ages of these

6. Kleine, F. K., in Final Report of the League of Nations International Commission on Human Trypanosomiasis, Geneva, 1928.

7. Homann, E.: "Germanin"-Behandlung bei multipler Sklerose, Deutsche med. Wchnschr. **55**:614 (April 12) 1929.

8. Veiel, F.: Die Behandlung des Pemphigus mit Germanin, München. med. Wchnschr. **78**:2047 (Nov. 27) 1931.

9. MacLean, G.: Dermatitis Associated with 'Bayer 205' Treatment of Rhodesian Trypanosomiasis, Ann. Trop. Med. **22**:531, 1928.

10. Gieseln, D. W.: Beitrag zur Behandlung des Pemphigus vulgaris mit Germanin, München. med. Wchnschr. **79**:1805 (Nov. 4) 1932.

patients varied from 13 years (Bohnstedt [11]) to 74 years (Grippain [12]). In most of the patients improvement, indicated by a drop in the temperature curve and a drying-up of the bullae, began after the third injection. In a few instances a second course was required. All the patients had previously been treated by several methods without results.

The failures reported by Daniels,[13] Bohnstedt [11] and Veiel [8] occurred in patients who had had severe exacerbations of pemphigus. Age was not a factor.

The effect of the drug on the clinical aspects of the disease may be summed up as follows: (*a*) A drop to normal in the irregular temperature curve; (*b*) a fall in the number of eosinophils (Mühlpfordt [14]); (*c*) a decrease in the retention of salts and water (Berggreen [15]); (*d*) a gain in weight.

If a dosage of 1 Gm. is not exceeded no untoward results should occur. The urine must be examined daily. If a flare-up of the eruption should occur, it may be considered in the nature of a Herxheimer reaction which also occurs in syphilis after small initial doses of arsphenamine. Generalized erythema has been reported by Gieseln [10] following daily injections and by Veiel [8] after the fourth injection. The erythema disappeared in a few days without sequelae.

Regarding the nature of the action of Bayer 205 in pemphigus the following theories may be advanced:

1. Any change in therapy often produces a remission. 2. The drug may act on the specific cause of the disease. 3. Since Bayer 205 has an effect on the coagulability of the blood, the improvement may be due to changes in the plasma or to cellular changes.

Sunder-Plassmann [16] questions the first theory because the bullae as a rule begin to disappear after the third injection. If the arrest of the disease is only a remission, no other treatment has, however, produced them for so long a period. Clinical improvement often goes hand in hand with serologic and hematologic improvement.

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11. Bohnstedt, R. M.: Zur Pemphigusbehandlung mit Germanin, München. med. Wchnschr. **80**:522 (April 7) 1933.

12. Grippain, P.: Zur Germaninbehandlung des Pemphigus vegetans, München. med. Wchnschr. **79**:2118 (Dec. 30) 1932.

13. Daniels, H.: Tödlicher Ausgang eines mit Germanin behandelten Falles von Pemphigus vulgaris, München. med. Wchnschr. **80**:524 (April 7) 1933.

14. Mühlpfordt, H. Germanin bei Pemphigus vulgaris und Dermatitis herpetiformis Duhring, München. med. Wchnschr. **79**:356 (Feb. 26) 1932.

15. Berggreen, P.: Pemphigus und Germanin, München. med. Wchnschr. **79**: 1842 (Nov. 11) 1932.

16. Sunder-Plassmann, O.: Bei Pemphigus Germanin? München. med. Wchnschr. **79**:1111 (July 8) 1932.

SUMMARY

1. A case of pemphigus vulgaris is reported occurring in a girl of 5 years following scarlet fever.

2. Remarkable clinical improvement followed the use of intravenous injections of Bayer 205.

3. Acute septicemia of undetermined origin developed soon after the end of the second course of treatment with Bayer 205 and the patient died.

4. The postmortem examination revealed acute endocarditis, acute toxic hepatitis and myocarditis.

5. A brief review of the literature on the therapeutic use of Bayer 205 is included.

Missouri Theatre Building.

Pediatric Biographies

BESSEJON DE LA CHASSAGNE

EIGHTEENTH CENTURY

A NOTE ON THE HISTORY OF DIABETES INSIPIDUS

JOHN RUHRÄH, M.D.
BALTIMORE

Toward the end of the seventeenth century, Thomas Willis,[1] in his work on "De diuresinimia, ejusque remedio, et speciatim de diabetes," called attention to the fact that there were two kinds of diabetes, one in which the urine tasted sweet and one in which it did not. Johann Peter Frank, in 1794, defined diabetes insipidus as an abnormally increased secretion of urine without sugar or disease of the kidneys. Two years previous to Frank, a Dr. Simmons,[2] in *"Medical Facts and Observations,"* noted two cases, one of which, reported by La Chassagne, is of great pediatric interest, as it concerned a young girl.

Of Bessejon de La Chassagne, I have been able to discover nothing except that he was a priest of St. Laurent.

The report of La Chassagne's case, taken from the translation as printed by Simmons, is as given here. A second case given by Simmons concerned a man who drank 3 gallons of water at night and 1 gallon in the day for twenty-three years.

AN ACCOUNT OF TWO CASES OF POLYDIPSIA OR EXCESSIVE THIRST

Almost all the modern nosologists have introduced into their systems a disease, to which, on account of the excessive thirst that forms its characteristic symptom, they gave the name of polydipsia; but in none of the examples of it they have been able to collect does it appear to have been idiopathic; and Dr. Cullen expressly says that it is almost always symptomatic. A very curious instance, however, of such an affection, apparently depending on a peculiarity of temperament, or what is called idiosyncracy, occurs in a woman now living in Paris, of whose case the first account was given by M. Bessejon de la Chassagne, in a letter which we shall here translate from the Paris *Journal* of May 1, 1789.

Paris, April 18, 1789.

To the Authors of the Journal.

Gentlemen:—You will interest equally the humanity and curiosity of the public, by inserting in your Journal the following anecdote, which, without doubt, will

1. Willis, Thomas: De diuresinimia, ejusque remedio, et speciatim de diabetes, 1682, section IV, chapter III.

2. Simmons: M. Facts & Observat. **2**:73, 1792.

be considered as a phenomenon. I have assured myself, with the most scrupulous accuracy, of the facts which I announce, but I leave to the reader to explain their nature and cause.

Catherine Bonsergent has been remarked from her tenderest years; a burning thirst, a drought without example, with which she has been continually afflicted from the time of her birth, has always fixed on her the attention of personal observation. Her parents, after having entrusted the first care of her to a nurse, took her home when she was three years old. It was not long before they observed that an extraordinary quantity of water was consumed in the house, and at length discovered that their daughter drank, every day, to the amount of two pailfuls. In summer she drank the first water she could meet with, in winter she had recourse to snow and ice, and she was always careful to reserve as much as would enable her to drink abundantly during the night.

At the age of 22 years, she married one, Gery, a cobbler, from whom she continued to conceal her complaint till after their marriage. She has had by him eight children, three of whom are still alive, and she is now pregnant with a ninth. What appears particularly extraordinary is, that during her lyings-in, instead of having recourse to such food and liquors as would seem most likely to strengthen her, she chooses rather, for the sake of satisfying her thirst, which at those times is more intense, to drink almost without interruption three or four quarts of coldest water. During the severe cold of last winter, this woman, who was then pregnant, drank to the amount of four pailfuls of water in 24 hours; and her husband being unable to afford the expense of such a consumption, was under the necessity of supplying her with melted snow and ice. This woman has never made use of any sort of strong liquors, and if she drinks only a single glass of wine, she feels an uneasy sensation in all her limbs and seems to be in danger of fainting. She is not dropsical; she even enjoys a pretty good state of health; she voids naturally all the water she drinks, but her urine is extraordinarily fetid. She lives at the Hôtel des Arts, Faubourg Saint Martin.

Signed, BESSEJON DE LA CHASSAGNE, Prêtre de St. Laurent.

Pediatrics in Art

DEVICES FOR WALKING

JOHN RUHRÄH, M.D.
BALTIMORE

There have been many devices contrived for aiding the child in learning to walk, and many of these have been depicted by various artists. One homely arrangement is shown here, as Rembrandt portrayed it in a simple but really remarkable print entitled "The Grandmother." Here

Early device to aid the child in walking as depicted by Rembrandt in "The Grandmother."

one sees what has been used throughout the ages to help the child learning to walk. A piece of cloth is attached to the child's clothing in such a manner that it serves as a support when held. Curiously enough this is not much in use at the present time. This picture is in the Cabinet of Prints at Stockholm. Another picture by Rubens, a drawing, now in the Louvre, shows a child learning to walk, and the outstretched arms and uncertain gait are well portrayed. A somewhat similar support is seen coming from about the level of the shoulders.

News and Comment

PERSONAL

Dr. J. Savoye has been named chief of the Pediatric Clinic at Lyons, France.

CORRECTION

In the article by Dr. Edward A. Boyden and Dr. Alice H. Fuller, entitled "Anatomy and Physiology of the Gallbladder in Children: A Cholecystographic Study," which appeared in the September issue (**48**:565, 1934), the heading of the last column of table 4, page 578, should read "Probability Integral" instead of "Probable Error."

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

DIFFERENTIATING SOME FUNCTIONS OF THE ANTERIOR PITUITARY HORMONES. OSCAR RIDDLE, Ann. Int. Med. **7**:23 (July) 1933.

The author isolated an anterior pituitary hormone in nearly pure form, together with the two other known hormones—the growth-stimulating and gonad-stimulating hormones. He attempts to associate certain responses of tissue with each of the three hormones. The active secretion of milk in mammals and the crop gland response in pigeons are thought to be specific responses to this third hormone.

READING, Galveston, Texas.

LYMPHOMATOSIS, MYELOMATOSIS, AND ENDOTHELIOMA OF CHICKENS CAUSED BY A FILTERABLE AGENT: I. TRANSMISSION EXPERIMENTS. J. FURTH, J. Exper. Med. **58**:253 (Sept.) 1933.

A filtrable virus obtained from a chicken suffering from a spontaneous type of lymphomatosis was used to inoculate a series of sixty-six chickens. There was a high incidence of "takes," with varying types of the disease showing in different animals. The following conditions were observed and were caused by a single filtrable agent free from viable cells: (1) lymphomatosis with or without tumor formation and with or without leukemia, (2) myelocytomatosis with or without leukemia and (3) endothelioma.

LUECKE, Dallas, Texas.

DO GLUCIDES FAVOR THE EVOLUTION OF EXPERIMENTAL XEROPHTHALMIA? G. MOURIQUAND and P. CHAIX, Compt. rend. Soc. de biol. **115**:538, 1934.

Bloch and Czerny found clinically in infants that a high proportion of glucides in a diet deficient in vitamin A tended to precipitate ocular lesions, especially xerophthalmia. In experiments on animals, however, xerophthalmia appeared regularly on the third day of the avitaminic regimen, independently of whether the diet was relatively rich or poor in glucides.

LEBENSOHN. [ARCH. OPHTH.]

SITE OF FORMATION OF THE SEX HORMONE IN THE HYPOPHYSIS. E. J. KRAUS, Beitr. z. path. Anat. u. z. allg. Path. **91**:245, 1933.

Granting that the hormone (prolan) which motivates maturation of the ovarian follicle and which is excreted in the urine of pregnant women is produced by the hypophysis, Kraus briefly reviews the evidence favoring the formation of the hormone by one or the other of the three types of cells of the hypophysis. He then presents the results of his histologic study of the hypertrophied hypophyses of seven nonpregnant women with carcinoma of the genital tract and of two women and five men with tumor of the brain. At necropsy urine from the bladder of four of the patients with carcinoma and of three of those with tumor of the brain gave a positive reaction for the hormone by the mouse test. Kraus interprets his findings as indicative of the formation of the hormone by the eosinophilous cells of the anterior lobe. While the mere weight of evidence may be so interpreted, it is to be noted that an individual case may speak just as strongly in favor of formation by one of the other two types of cells. He next presents the results of a series of implantations of bits of the normal and the adenomatous human hypophysis into immature mice. These results, Kraus thinks, indicate that the

hormone may be formed by either type of chromophil. Determination of the source of the hormone in pregnancy requires further research.

SCHULTZ. [ARCH. PATH.]

Nutrition

THE INCISOR TEETH OF ALBINO RATS AND GUINEA PIGS IN VITAMIN A DEFICIENCY AND REPAIR. S. B. WOLBACK and P. R. HOWE, Am. J. Path. **9**:275, 1933.

The initial effect of a deficiency in vitamin A on the incisor teeth of rats and guinea-pigs is on the enamel organ. The ameloblasts atrophy, then the remainder of the organ atrophies; finally, metaplasia, calcification and, in the guinea-pig, ossification occur. Atrophy and depolarization of odontoblasts follow changes in the enamel organ. The odontoblasts survive longest on the side (labial), where in apposition to the enamel organ, after long-continued experiments, gross deformities result in rats from the complete or partial failure of dentine formation. Two types of denticles are described, one built up by depolarized odontoblasts, the other formed by inclusion of ameloblasts by the folding of imperfectly formed dentine at the formative end of the tooth. Defective formation of enamel and other poorly understood conditions in teeth, such as denticles, pulp bone and cementicles, may reasonably be regarded in the human being as expressing a possible deficiency in vitamin A. Our observations indicate that in the incisor teeth of rodents the odontoblasts are influenced throughout life by the enamel organ. As in other morphologic problems concerning deficiencies in vitamins, study of the sequences of repair was essential. We emphasize the importance of two types of material for control, the normal and the progressive stages in repair. Our observations indicate that deficiency in vitamin A is the most important of the known vitamin deficiencies, in its effect on the formation of teeth.

FROM AUTHORS' SUMMARY. [ARCH. PATH.]

THE UNDERNOURISHED CHILD. HOWARD L. EDER, Arch. Pediat. **50**:628 (Sept.) 1933.

One hundred and twenty cases of malnutrition cared for in a preventorium were investigated. Eder discusses the routine of the institution in detail. He considers care in a preventorium to be the most effective way to combat the difficulties of the undernourished child, and thinks that it is of lasting value in a large percentage of the cases.

WADDELL, JR., University, Va.

INFANT FEEDING AND SUMMER CARE. W. H. CRAWFORD, Arch. Pediat. **50**:642 (Sept.) 1933.

The article offers nothing new.

WADDELL, JR., University, Va.

OSSEOUS DEVELOPMENT AS AN INDEX OF METABOLIC SPEED. E. K. SHELTON, Endocrinology **17**:667 (Nov.-Dec.) 1933.

This article deals particularly with the mentally subnormal and emotionally unstable child. Shelton is of the opinion that any metabolic disorder in childhood which is sufficiently severe to produce mental or emotional symptoms will be reflected in the osseous development. He cites the case of three siblings with retarded carpal development, two of whom were treated with a thyroid preparation and the third by the addition of a high content of vitamins A and D to the diet. The two treated with a thyroid preparation gained rapidly in carpal development as related to chronological age, and the remaining sibling, without thyroid therapy, lost. Another child lost consistently in carpal development as related to age

over a five year period; then on receiving a thyroid preparation, he made a gain in one year commensurate with that of a normal child over a period of three years.

A study was carried out in the first four grades of certain schools in Santa Barbara, Calif. Roentgenograms of the wrist of each of the students, five hundred and sixty children in all, were secured. Twelve and five-tenths per cent were found to have retardation of carpal development of two or more years' standing. Two years later it was learned that one third of the children selected during this interval by the instructors as needing the services of the clinic for child guidance because of various abnormal behavioristic tendencies came from this group comprising only 12.5 per cent of the student body. The conclusion is that the developmental status indicated by the degree of carpal unfolding is important in an intelligent selection of mentally subnormal and emotionally unstable children for the thyroid substitution regimen.

JACOBSEN, Buffalo.

VITAMIN D DEFICIENCY. HARRY BAKWIN and RUTH MORRIS BAKWIN, J. Pediat. **3**:880 (Dec.) 1933.

Five infants with tetany but with no roentgenographic signs of rickets had convulsions, low blood calcium and increased electrical irritability of the muscles. Antirachitic measures promptly cured the tetany and elevated the blood calcium to normal levels.

LEMASTER, Evanston, Ill.

CONGENITAL STEATORRHEA. E. A. COCKAYNE, Lancet **2**:1086 (Nov. 11) 1933.

Cockayne reports the case of a girl, aged 1 year and 10 months, who had been fed a prepared food for infants for the first ten months. After the age of 10 months she was given a mixed diet. She then began to have loose "butter stools." During hospitalization the stools were chocolate-colored, others were typical "butter stools," and all had a rancid odor. While on an ordinary diet, the fat content of which was not accurately known, the fat percentage varied from 43 to 72, the fatty acid from 39 to 57 and the neutral fat from 41 to 60. The levulose tolerance test showed the blood sugar to be 109 per cent of normal before the test, 107 at the end of one hour, 146 at the end of two hours and 199 at the end of four hours. Cockayne cites three families in which this error of metabolism has been recorded. The nature of the error is still unknown.

LANGMANN, New York.

THE CHEMISTRY OF FLESH FOODS AND THEIR LOSSES ON COOKING. R. A. MCCANCE and H. L. SHIPP, Medical Research Council, Spec. Rep. Ser. no. 187, London, His Majesty's Stationery Office, 1933.

Extensive analyses were made of all kinds of fish, meats and fowl for their constituents: total nitrogen, purine nitrogen, nonprotein nitrogen, extractive nitrogen, fat, carbohydrates, chlorides, total and inorganic phosphorus, sodium, potassium, calcium, magnesium and iron. Of chief interest are the changes in meat caused by various methods of cooking. Part I gives a detailed explanation of the technic of each analysis, part II contains the results of the analyses, and part III includes a study of the losses brought about by cooking. The entire work has been carefully and thoroughly presented and should be a standard for reference on this subject. While the report should be of value to all persons interested in the composition of flesh foods, the third part will be of special interest to those interested in the science of cooking or engaged in the teaching of it or in the sale of ovens or other cooking appliances.

LEMASTER, Evanston, Ill.

SCURVY TREATED WITH ASCORBIC ACID. LEONARD G. PARSONS, Proc. Roy. Soc. Med. **26**:1533 (Oct.) 1933.

A girl, aged 9 months, was admitted to the hospital with scurvy. She had been fed sterilized milk and had not had any fruit juice. She was given ascorbic

acid in the hospital, and the same diet was continued. The symptoms commenced to clear up in a week, and the child was convalescent in ten days. She was given 350 mg. of ascorbic acid, the equivalent of 17½ ounces (517 cc.) of orange juice.

WILLIAMSON, New Orleans.

FEVER FOLLOWING SWEETENED CONDENSED MILK. M. COFFIN, Bull. Soc. de pédiat. de Paris **30**:570 (Nov. 15) 1932.

A boy was given feedings of sweetened condensed milk when 4 months old. Previous to that time he was breast fed. He began to have a moderate fever, morning and night. Soon vomiting occurred and gradually became worse. He gained weight almost throughout the period of fever. When instead of the sweetened condensed milk he was given buttermilk and then mixtures of fresh cow's milk, there was no fever. Whenever the feeding of sweetened condensed milk was resumed fever invariably ensued. Coffin thinks that the fever is similar in nature to that occurring in some infants when they are fed dried milk. The latter do not exhibit symptoms of indigestion, but, despite the presence in his patient of anorexia, vomiting and, on one occasion when some condensed milk was added to the buttermilk, diarrhea, Coffin insists on calling the case one of "alimentary" fever rather than "dyspeptic" fever.

BENJAMIN, Montreal, Canada.

"TOURNESOL" FLOUR AND MARKED DIGESTIVE HYPERSECRETION WITHOUT GASTRIC STASIS. M. LEVESQUE and SUZANNE DREYFUS, Bull. Soc. de pédiat. de Paris **30**:665 (Dec. 20) 1932.

A number of infants who had persistent abdominal pain, especially marked when taking their feedings or soon afterward, were relieved when they were fed a vegetable protein flour called "farine de tournesol." They all had some digestive symptoms such as vomiting, diarrhea and salivation, in addition to the colicky pain, and were usually pale during the periods of pain. The stomach emptied rapidly, and the contents after fasting usually consisted of excessive mucus, with or without hyperchlorhydria. The pathogenesis of the digestive disturbances is not known. It is thought that the vegetable protein flour had some sedative effect on the digestive tract in these infants, who seemed to have hypervagotonia.

BENJAMIN, Montreal, Canada.

THE COMMON FORMS OF AVITAMINOSIS. L. RIBADEAU DUMAS and R. MATHIEU, Paidoterapia **12**:207 (July) 1933.

Complete avitaminosis is rarely seen in Spain, but lack of single vitamins is common. The authors review each vitamin in turn and give a complete summary as to etiology, symptoms, diagnosis and treatment in cases of deficiency. They believe in the prevention rather than in the cure of avitaminosis.

HERRON, Spokane, Wash.

UPSETS OF THE METABOLISM OF CALCIUM IN INFANCY AND TREATMENT. BAUDILIO DANÉS, Paidoterapia **12**:441 (Sept.) 1933.

Danés intends to prove that many physicians are overinfluenced by the results obtained in modern investigations of the metabolism of calcium and accordingly apply the wrong treatment for disturbances of this metabolism. The present method of treatment of tetany, rickets, spasmophilia and the like does not produce the perfect result wished for because the physician often does not have in mind a clear clinical picture of these diseases and forgets the factors that underlie disturbances of the metabolism of calcium. The factors concerned in the metabolism of calcium are complex, and this must be borne in mind in the treatment of these disturbances.

HERRON, Spokane, Wash.

THE INORGANIC AND ACID-SOLUBLE ORGANIC PHOSPHORUS OF THE BLOOD SERUM IN SPONTANEOUS AND IN EXPERIMENTAL RICKETS. V. ANGELINI, Riv. di clin. pediat. **31**:1153 (Oct.) 1933.

The blood serum of twenty-nine infants with rickets contained, on the average, 2.29 mg. of inorganic phosphorus and 1.22 mg. of acid-soluble organic phosphorus per hundred cubic centimeters; that of ten healthy infants, 3.75 mg. and 0.01 mg. per hundred cubic centimeters.

The blood serum of rats with experimental rickets contained, on the average, 2.56 mg. of inorganic phosphorus and 2.81 mg. of acid-soluble organic phosphorus per hundred cubic centimeters. Healthy rats used as controls gave 6.20 mg. and 2.10 mg. per hundred cubic centimeters, respectively. The rickets was produced by a diet poor in phosphorus.

While the total acid-soluble phosphorus of the serum in human rickets and in experimental rickets in rats is diminished from normal, and the inorganic phosphorus is similarly diminished, the organic phosphorus is not diminished, but shows a tendency to be increased. These data suggest a possible pathologic basis of rickets, namely an inability of the rachitic organism to change organic phosphorus to inorganic.

HIGGINS, Boston.

INFLUENCE OF ULTRAVIOLET RAYS ON THE AMOUNT OF PHOSPHATE IN THE BLOOD OF THE FASTING ANIMAL. R. DELLA GIUSTINA, Riv. di clin. pediat. **31**:1205 (Oct.) 1933.

In fasting rabbits Giustina found that in seventy-two of eighty-two observations the blood phosphate was increased following irradiation of the animal with ultraviolet rays. With the mere prolongation of the fast, i. e., in the nonirradiated animals, the phosphate of the blood steadily decreased.

HIGGINS, Boston.

THE COMPLEX: I. THE RÔLE OF THE PARATHYROID GLANDS IN THE REGULATION OF CALCIUM AND POTASSIUM IONS; II. THE RÔLE OF THE DIGESTIVE GLANDS AND THE LIVER IN THE REGULATION OF THE CALCIUM AND POTASSIUM IONS; III. THE RÔLE OF THE SUPRARENAL GLANDS AND THE COMPLEX OF THE GLANDS OF INTERNAL SECRETION ON THE REGULATION OF THE CALCIUM AND POTASSIUM IONS. I. R. BACHROMEJEV, Arch. f. d. ges. Physiol. **231**:426, 441 and 449, 1932.

The potassium and calcium of the blood can be markedly affected by various nervous influences and by injection of pharmacodynamic substances (e. g., atropine and epinephrine). There is thus a complex glandular-nervous-internal secretory regulation of these ionic constituents.

KUGELMASS, New York.

RICKETS HEALED WITHOUT ULTRAVIOLET RAYS. A. LOESCHKE, Monatschr. f. Kinderh. **59**:97, 1933.

The point of view of Loeschke is rather confusing. One gets the impression, which cannot be correct, that he believes rickets to be curable only by ultraviolet rays; but he reports excellent results in treatment from the use of a German proprietary remedy which seems to contain all the known vitamins, organic extracts and minerals that it is possible to obtain.

GERSTLEY, Chicago.

ACID GRUEL IN NURSLINGS' DYSPEPSIA. C. WIENER, Monatschr. f. Kinderh. **59**:117, 1933.

An attempt was made to introduce rice gruel acidified with 8 cc. of 10 per cent lactic acid per liter, giving a p_H of 4.5, in the treatment of dyspepsia. Little can be said for the indications for this treatment, or for the results submitted by Wiener. He does not understand why acid added to gruel often intensifies the diarrhea, whereas the same acid added to cow's milk is beneficial.

GERSTLEY, Chicago.

THE EXCRETION OF IRON IN HUMAN URINE UNDER PHYSIOLOGIC AND PATHOLOGIC CONDITIONS. F. LANYAR, H. LIEB and A. VERDINO, Ztschr. f. physiol. Chem. **217**:160, 1933.

The observation of Lintzel (*Chem. Abstr.* **22**:3424, 1928) that normal human urine contains no iron (less than 0.01 mg. per liter) is corroborated. The excretion of iron is therefore not effected through the kidneys. Only after parenteral injection is iron thus excreted. Intravenous injection of from 1.5 to 2 mg. of iron as Fe^{III} NH_4 citrate gave a barely demonstrable trace in the urine, and a preparation of colloidal iron required an injection of 4 mg. for subsequent detection. Even in pathologic cases, including fever, diabetes, erythrocytosis vera, pernicious anemia, hemolytic icterus and probably nephrosis, no renal excretion of iron occurs.

KUGELMASS, New York.

VITAMIN D: IV. ERGOSTEROL IN SOY-BEAN OIL AND THE ECONOMIC VALUE OF THE SOY-BEAN OIL AS A SOURCE OF VITAMIN D. SEIICHI IZUME, YOSHINORI YOSHIMARU and TEI HIDAKA, J. Agric. Chem. Soc. Japan **9**: 246, 1933.

The soy bean oil was saponified by being boiled with two normal potassium hydroxide in alcoholic solution for six hours. The unsaponifiable matter was extracted with ether and the ether extract evaporated. A brown semisolid was obtained which was crystallized. It gave ergosterol reactions. The acetate of ergosterol was prepared; it melted at from 131 to 132 C. (267.8 F. to 269.6 F.). The content of ergosterol in sterol crystal was from 19.8 to 20 per cent from the analysis by the absorption spectrum. Soy bean oil and the sterol crystal were irradiated with ultraviolet rays. These substances were sufficient to cure mice of rachitis with daily doses of 0.1 and 0.01 mg., respectively. Ergosterol may not come from the materials of soy (the bean and the whest) but may be synthesized by Aspergillus oryzae. The preparation of ergosterol from soy bean oil has great economic value.

KUGELMASS, New York.

Prenatal Conditions

UROGRAPHY IN ANOMALIES OF THE URINARY TRACT IN INFANTS AND CHILDREN. MEREDITH F. CAMPBELL, Am. J. Roentgenol. **28**:12 (July) 1932.

In the order of frequency, the indications for urologic examination in juveniles are pyuria, hematuria and pain, and in practically all of the examinations urography, i. e., cystography or pyelography, must be resorted to. The various anomalies are enumerated with the aid of roentgenograms and, in some instances, photographs of postmortem specimens. In juveniles, anomalous developments of the urinary tract are commonly the etiologic factor when persistent infection exists. By urography nearly all of these anomalies may be demonstrated and diagnosed. The roentgenographic diagnostic criteria are identical with those employed when the patient is an adult. Urograms of the common anomalies are presented, and the impossibility of accurate urologic diagnosis without urography, especially in infants and children, is demonstrated.

STULIK, Chicago.

FAMILIAL CLUBBING OF FINGERS AND TOES; REPORT OF A CASE. OSCAR B. RAGINS and E. B. FREILICH, Ann. Int. Med. **6**: 946 (Jan.) 1933.

A review of the literature revealed no similar reports. The patient was a man, aged 34, who presented himself for physical examination. Aside from the clubbing of the fingers and toes and a tic of the palpebral muscles of the left eye, nothing abnormal was found on physical examination. The heart and lungs were normal. The patient's sister, father and paternal uncle also presented the same findings. In this case the clubbing affected mainly the soft tissue, with little variation from the normal in the distal phalanges.

READING, Galveston, Texas.

A Case of Trilocular Biventricular Cardiopathy. E. Jaso and P. Bernal Fandos, Arch. de méd. d. enf. **36**: 736 (Dec.) 1933.

These Spanish clinicians report a case of trilocular biventricular cardiopathy in an abandoned infant, aged 15 months, at the Provincial Institute for Puericulture in Madrid. Death resulted within a few days, and autopsy revealed many astonishing anatomic deviations. There were anomalies in the venous distribution, the jugular and the subclavian veins on either side uniting to form a brachycephalic trunk descending into the thorax anterior to the pulmonary artery and veins and emptying into the superior portion of the auricle. The pulmonary artery measured 47 mm. in circumference. The heart contained but one large auricle, the normal partition being represented by a small muscular pillar on the anterior surface; the interventricular septum showed a major defect in the upper portion. The single auricle communicated with both ventricles through an oval aperture 31 mm. in diameter, the valves closing this orifice consisting of an anterior, posterior and lateral leaf. Both ventricles were concentrically hypertrophied, and the total weight of the heart was 75 Gm., or nearly three times the normal for the body weight. An exhaustive discussion of the embryology concludes the report.

Amesse, Denver.

Congenital Lacunae of the Cranial Vault in a Child Aged Five Years: Familial Character. Marcel Lelong and Bosquet, Bull. Soc. de pédiat. de Paris **30**:161 (March 15) 1932.

A boy, 5 years old, was found to have two oval areas that were not calcified in the vault of the skull. They were situated just behind the bifurcation of the lambdoid suture, one on each side of the midline, and separated by a narrow strip of bone. These areas could be palpated; there was pulsation in them, and an impulse could be felt when the child coughed. The integument over them appeared to be normal. There were no other abnormal physical findings, and the remainder of the skeleton was normal. The blood phosphorus, calcium and sugar were normal. No polyuria was present. The Wassermann reaction of the blood was negative. The tuberculin reaction was positive. Roentgenograms of the skull are included in the communication. An interesting feature was the familial character of the condition; it was present in the mother, and she related that her father had also had soft areas in the skull. The father and three other children in the family did not show the defect.

Benjamin, Montreal, Canada.

Multiple Bony Malformations. E. Sorrel, A. Richard and Le Grand-Lambling, Bull. Soc. de pédiat. de Paris **30**:167 (March 15) 1932.

A boy, 3 years old, presented three congenital malformations of the skeleton: (1) absence of the right radius and the corresponding metacarpal and phalangeal bones, (2) elevation of the left scapula and (3) crowding and apparent fusing of the upper cervical vertebra, so that there appeared to be only five cervical vertebrae, with anterior rachischisis from above continuing through the upper dorsal vertebrae. Corresponding to these bony malformations, there were deformities of the right arm and hand, the left shoulder and the neck.

Benjamin, Montreal, Canada.

Triple Congenital Malformation of the Lower Extremities. E. Sorrel and Le Grand-Lambling, Bull. Soc. de pédiat. de Paris **30**:169 (March 15) 1932.

A girl, 3 months old, presented three congenital bilateral deformities of the lower extremities, viz., clubfoot, genu recurvatum and dislocation of the hip.

Benjamin, Montreal, Canada.

CONGENITAL DEXTROCARDIA WITH MULTIPLE CONGENITAL ORGANIC IMPERFECTIONS. ANTONIO CELENTANO, Pediatria **42**:57 (Jan. 1) 1934.

The various types of dextrocardia are briefly described, and an isolated case is reported in a boy, aged 6 years. In this case the Wassermann and von Pirquet reactions were both positive. The anomalous position was complicated by multiple congenital imperfections. The author reports the results of the roentgenographic and electrocardiographic observations and states that, in his opinion, the symptom complex suggests the existence of a defect of the interventricular septum associated with persistence of the duct of Botallo.

SIGNORELLI, New Orleans.

MALFORMATIONS OF THE HAND AND FOOT AND THEIR FORMAL GENESIS. G. POLITZER, Fortschr. a. d. Geb. d. Röntgenstrahlen **43**:605 (May) 1931.

Politzer describes fourteen cases of malformations of the hands and feet, consisting chiefly of numerical and morphologic variations. He includes several roentgenograms and drawings for illustration. The changes in form are discussed, and the genesis is explained on the basis of an embryonic maldevelopment. Amniotic twists or abnormal underdevelopment of the amnion apparently does not enter the process.

STULIK, Chicago. [MORGAN, Am. J. Roentgenol.]

SIGNS OF INJURY TO THE FETUS. A. MAYER, München. med. Wchnschr. **80**: 1535 (Oct. 6) 1933.

It may be extremely difficult to recognize signs of impending danger to the fetus. As a rule, the danger is exaggerated. Mayer found that in most cases in which forceps were used because of fetal indications the new-born baby was energetic after delivery, showing that its life had not been endangered. In spite of these facts, the physician who is prepared for an instrumental delivery applies forceps, no matter how difficult the procedure happens to be. The result is often a badly injured mother and a dead child. In these cases waiting would be better than the treatment. Much harm that is done by early intervention can be prevented by waiting.

BRAHDY, Mount Vernon, N. Y.

UNUSUAL FORMS OF FAMILIAL OSTEOCHONDRODYSTROPHY. T. DALE, Acta radiol. **12**:337 (Sept. 30) 1931.

The author describes three unusual cases of a systemic disease of the skeleton which he calls "osteochondrodystrophy." The disease is familial. Two of the patients were brother and sister, and the third had a brother who presented the same condition. The patients showed dwarfism, pigeon breast and kyphosis; the limbs were remarkably long and well developed. The most important changes in the bones were defective ossification of the bodies of the vertebrae with kyphosis and scoliosis, defective development of the epiphysis of the head of the femur, widening of the acetabulum and minor changes in the shoulder and knee joint suggesting local malacia. In two of the cases there was also defective development of the epiphyseal centers in the distal ends of the forearms and in the metacarpals.

The author compares his cases of osteochondrodystrophy with those described in three papers by Morquio, Ruggles and Brailsford. In contradiction of the latter he shows that the skeletal changes in the extremities were markedly different in the different cases. A comparison with chondrodystrophy shows considerable difference between the two conditions. Dale suggests that the disease is due to some abnormal endocrine function, and that it is a condition intermediate between achondroplasia and local malacia. Plates are given showing roentgenograms.

STULIK, Chicago. [MORGAN, Am. J. Roentgenol.]

Acute Infections

A Comparison of Schick Tests with Freshly Diluted and Stabilized Toxins. H. E. Thelander, Arch. Pediat. **50**:373 (June) 1933.

The writer compares the advantages of the newer preparation for the Schick test with the old freshly diluted toxin. One hundred and ninety-five persons were tested with old freshly diluted and with new already diluted toxin, the results of the two tests being identical in 83 per cent. The chief disadvantage of the ready-diluted toxin appeared to be the occurrence of pseudoreactions in 16 per cent of children and 20 per cent of adults. So marked and persistent were some of these pseudoreactions that if these tests alone had been considered a reading of "pseudonegative" would not have been made. For this reason the writer believes that until a diluent is found that gives a lower percentage of pseudoreactions than the diluent now used, the old material freshly diluted with physiologic solution of sodium chloride remains the more accurate of the various materials.

Waddell, Jr., University, Va.

Occurrence of the Bordet-Gengou Bacillus. B. Kristensen, J. A. M. A. **101**:204 (July 15) 1933.

Kristensen's examinations corroborate the hypothesis that the Bordet-Gengou bacillus is the etiologic agent of whooping cough. The best method for making early diagnoses is that employing a cough plate. An isolation period of four weeks after the onset of a typical paroxysm has been found sufficient in practice. Healthy carriers have not been found outside of families in which whooping cough exists. Abortive or atypical cases play an important rôle in the spread of the disease.

Bonar, Salt Lake City.

Report on a Group of Fifty Children Dick-Tested Eight Years after Immunization Against Scarlet Fever. H. G. Ball, J. A. M. A. **101**:363 (July 29) 1933.

In 1925 eighty-three children who showed a positive reaction to the Dick test were immunized against scarlet fever. In 1933 fifty of these children were retested, and thirty-two reacted negatively while eighteen showed a slightly positive reaction. Of twenty-two who had received only three doses of dilute toxin, twelve showed a slightly positive reaction. Of twenty-eight who had received five or six doses, only six showed a slightly positive reaction. Dilute toxin, given in adequate doses, confers immunity on a high percentage of persons susceptible to scarlet fever.

Bonar, Salt Lake City.

Heterologous Scarlet Fever. J. D. Trask and F. G. Blake, J. A. M. A. **101**:753 (Sept. 2) 1933.

It has been established that heterogenicity exists among the toxins derived from scarlet fever streptococci. Trask and Blake demonstrated and studied a new scarlatinal toxin from the body fluids of patients with scarlet fever who had failed to respond to a potent scarlatinal antitoxin. In order to combat heterogenicity of scarlatinal antitoxins a polyvalent antitoxin was prepared which neutralizes the new toxin. Polyvalency is desirable in therapeutic scarlatinal antitoxin.

Bonar, Salt Lake City.

Effect of Tonsillectomy on the Development of Immunity to Scarlet Fever. Camille Kerezlein and William H. Park, J. A. M. A. **101**:764 (Sept. 2) 1933.

In the limited number of cases studied, tonsillectomy had no marked effect on susceptibility to scarlet fever within six months after it had been done, as demonstrated by the changing of a positive reaction to the Dick test into a negative one.

Bonar, Salt Lake City.

COLONY FORMATION OF DIPLOCOCCUS RUBEOLAE (MEASLES). RUTH TUNNICLIFF, J. Infect. Dis. **52**:39 (Jan.-Feb.) 1933.

This is a technical discussion of the appearance of the colonies of Diplococcus rubeolae, which Tunnicliff believes to be the etiologic factor in measles.

TOOMEY, Cleveland.

WHOOPING COUGH: RÉSUMÉ OF A SEVEN YEARS' STUDY. LOUIS W. SAUER, J. Pediat. **2**:740 (June) 1933.

The use of cough plates in the early diagnosis of pertussis is advocated, and their preparation is described. The results obtained by the author in the experimental transmission of pertussis to monkeys are briefly discussed. The site of the lesion in pertussis is chiefly in the smallest bronchioles, contrary to the older accepted idea that the trachea and large bronchi were the seat of the characteristic lesion. The blood picture is seldom an aid in early diagnosis, because the typical lymphocytosis does not appear, as a rule, until the paroxysmal stage is well established. The author was successful in demonstrating bacteriophage of Bacillus pertussis by growing young cultures of old strains in a concentrated, fresh sewage bouillon containing a small amount of defibrinated blood. Excellent results are reported from the use of injections of fresh vaccine in producing prolonged immunity in children.

LEMASTER, Evanston, Ill.

THE PRESENT STATUS OF SERUM TREATMENT IN ACUTE POLIOMYELITIS. CONRAD WESSELHOEFT, J. Pediat. **3**:330 (Aug.) 1933.

The author has collected data from a wide variety of sources showing the results obtained in the treatment of poliomyelitis by various methods. Although there is tangible proof of the presence of specific immune bodies in the serum of persons convalescent from poliomyelitis and in a high percentage of the serums obtained from normal adults as shown from laboratory experiments, there is no positive proof from this compilation of statistics or from controlled clinical experiments that such serums are efficacious after the preparalytic stage is once manifested. The question of the dosage of the serum and the preferred route of administration cannot be settled definitely at the present time. The author is uncertain whether Rosenow's experimental work on poliomyelitis will be eventually substantiated.

LEMASTER, Evanston, Ill.

THE BLOOD PICTURE IN THE EARLY STAGES OF PERTUSSIS. VERA B. DOLGOPOL, J. Pediat. **3**:367 (Aug.) 1933.

In five cases the author made blood counts twice weekly for twenty-one days before the onset of whooping cough and also through the catarrhal and paroxysmal stages. In the catarrhal stage the total white cell count and the percentage and absolute number of lymphocytes did not rise above the usual figures for the child. At the onset of the spasmodic stage the total white cell count rapidly increased. The percentage and total number of lymphocytes also rose quickly. Although the percentage of neutrophils was decreased, their total number per cubic millimeter of blood remained the same or increased slightly.

LEMASTER, Evanston, Ill.

POSTVACCINAL ENCEPHALITIS. SAMUEL NEWMAN, J. Pediat. **3**:461 (Sept.) 1933.

At the present time seventy-four cases of postvaccinal encephalitis have been reported in the United States. The occurrence of this complication in other countries is mentioned. In regard to the etiology, the two leading hypotheses are that the condition is due to activation of a latent virus, and that the vaccine virus itself causes the disease; but neither can be regarded as proved. Certain definite

histologic findings are present to disinguish this type of encephalitis from epidemic encephalitis. The best known means of prevention consist of vaccinating the child when less than 1 year of age and only when he is in apparently good health and of making the puncture of the skin with a minimum of trauma. There is experimental proof that previous immunization with diphtheria toxoid lessens the chance of postvaccinal encephalitis. One case report is presented.

LEMASTER, Evanston, Ill.

BRUCELLA ABORTUS INFECTION IN EARLY INFANCY. MAURICE M. FLIESS, CLIFTON FORGE and J. V. JORDAN, J. Pediat. **3**:502 (Sept.) 1933.

Infection with Brucella abortus in a 9 month old baby who had been sick for two months is reported. Infection with Brucella abortus was suspected because of irregular fever, profuse sweats when asleep, negative results of physical examination and leukopenia. The blood culture was positive for Brucella abortus, and the agglutination test was positive in a dilution of 1:180. The infant had been fed unboiled cow's milk for a month before becoming ill. Two weeks after beginning a diet based on a formula of evaporated milk, the infant appeared perfectly recovered.

LEMASTER, Evanston, Ill.

THE USE OF WHOLE CITRATED BLOOD INTRAMUSCULARLY IN A MEASLES EPIDEMIC. ROBERT M. LORD, J. Pediat. **3**:509 (Sept.) 1933.

Eighty-nine children exposed to measles were given an injection intramuscularly of citrated whole blood obtained from the parents or from convalescent brothers and sisters. The resulting measles in every case was mild, of short duration and without complications. The author prefers to wait a few days after exposure before injecting the blood, so that a mild attack of measles will develop in the child. Thereby the child will be protected permanently. If the blood is injected immediately after exposure, the child does not contract measles, but at a later date he may suffer a severe attack with complications, if he has an unrecognized exposure and is not protected again. There is also a psychologic advantage in using blood from the patient's own family rather than serum from unknown donors.

LEMASTER, Evanston, Ill.

FINISHING THE JOB IN DIPHTHERIA PREVENTION. D. B. ARMSTRONG, M. J. & Rec. **138**:47 (July 19) 1933.

To show what has been accomplished in the prevention of diphtheria in New York State, the author gives the following figures for the year 1925, the year before the five year demonstration period, and for the year 1932: In the up-state area there were only 62 deaths from diphtheria in 1932, as compared with 260 in 1925. In this year the death rate was 1 per hundred thousand, as compared with 64 in 1925—a reduction of nearly 85 per cent. During the first three months of 1933 there were only 18 deaths from diphtheria up-state, or less than half the number for the corresponding period in 1932.

It is encouraging to note similar evidence in national experience. According to the records of 17,000,000 industrial policy holders of the Metropolitan Life Insurance Company, the mortality from diphtheria was at the minimum for all time in 1932. The slogan of "no more diphtheria" has not been reached, but progress has been made.

The first stage of the fight against diphtheria was the early school campaign; the second was the preschool campaign; the third must be with the infants as they are losing their congenital protection.

Certain steps must be taken in the third campaign. First, the family physician must be urged to play a greater part in the immunization of the infant in the home; second, the department of health must keep up a permanent program; third, the state board of health must watch for areas where the death rate is

high and must work there; fourth, the state department of health must recognize private health groups and medical groups and must be willing to lend assistance, and fifth, the experiments which are being made to have only one injection necessary for immunization must be carried on.

The continuance of these efforts will place diphtheria alongside of yellow fever, malaria and smallpox in the museum of rapidly disappearing diseases.

WILLIAMSON, New Orleans.

REVIEW OF THE USE OF IMMUNE SERUM IN ACUTE POLIOMYELITIS. JAMES M. SMELLIE, Arch. Dis. Childhood **8**:75 (Feb.) 1933.

The diagnosis of poliomyelitis in its acute or preparalytic stage is an essential criterion for successful treatment by immune (convalescent) human serum. This preparalytic stage presents a chain of symptoms and physical signs which can be recognized. Lumbar puncture, with cytologic and biochemical examination of the cerebrospinal fluid, is necessary to establish the diagnosis, and immune serum should not be administered until this has been done. The employment of convalescent serum in the treatment of acute poliomyelitis is founded on sound experimental data in animals. It has been demonstrated that the serum of a person who has had poliomyelitis possesses high neutralizing properties for many years thereafter. Further, the blood of adults who have not suffered from the disease clinically may also possess neutralizing properties. While the statistical evidence in favor of immune serum is far from convincing, those who have had most experience with this form of treatment believe that a strong case has been made out for its employment and that ample justification exists for its continued and extended use. The place of lumbar puncture in the treatment of preparalytic poliomyelitis has not yet been settled. The withdrawal of sufficient fluid to allow the pressure to return to normal is probably of value in preventing the development of paralysis or, at least, in modifying its progress. Evidence is accumulating to show that passive immunization against poliomyelitis may be of value as a prophylactic measure.

KELLY, Milwaukee.

ANTITOXIN IN THE TREATMENT OF SCARLATINA, WITH SPECIAL REFERENCE TO THE PREVENTION OF COMPLICATIONS. ALEX H. IMRIE, Glasgow M. J. **119**:36 (Feb.) 1933.

The cases were divided into cases of simple, septic and toxic scarlet fever. The untreated control group numbered 1,322 patients, of which 337 had moderate or severe cases. Two hundred and ninety-four patients were treated. Antitoxin had a beneficial effect on the initial toxemia, and reduced slightly the rash and pyrexia, if given early. It had no effect on well established toxemia. The number of complications in the patients treated was less if the antitoxin was given before the fourth day of the illness. Intravenous administration was dangerous. There was collapse, and severe reactions were noted, in spite of a previous subcutaneous desensitization.

SNELLING, Toronto, Canada.

THE DIASTATIC INDEX IN ACUTE PAROTITIS. GAVIN A. DUNLOP, Lancet **2**:183 (July 22) 1933.

This is a brief report on the constant finding of an increased amount of diastase in the urine of patients afflicted with mumps. This is comparable in degree with that found in acute pancreatitis, and the author wonders whether pancreatitis occurs more frequently in mumps than is commonly supposed. He makes it a rule that no patient with mumps shall be allowed to mix with others until the urinary diastase has returned to normal, which may be some days after the swelling has subsided.

LANGMANN, New York.

NERVOUS COMPLICATIONS OF WHOOPING COUGH. A. SANTILLANA, Arch. de méd. d. enf. **36**:474 (Aug.) 1933.

It would appear from a perusal of the literature concerned with infectious diseases that the neurotropic affinity of the virus of whooping cough is noted with increasing frequency.

Comby was the first (in 1905) to describe acute nonsuppurative encephalitis following vaccination; since that period many instances have been described in the course of such invasions as measles, chickenpox, influenza and typhoid fever. Among sixty-two cases reported by Comby, seven were sequels of whooping cough, the virus of which is prone to attack the central nervous system in the form of polyneuritis, myelitis or other syndromes of major significance. Recovery is likely to be followed by psychic or psychomotor phenomena.

The author reports two fatal cases of encephalitis following pertussis.

AMESSE, Denver.

DYSENTERY IN INFANCY AND EARLY CHILDHOOD. J. SURANYI, Bull. Assoc. internat. de pédiat. prévent. **1**:15, 1933.

The author reviews the recent report of Professor Hainiss of the University of Budapest on the prophylaxis of dysentery. The summer and autumn diarrheas of infants are, for the most part, frankly dysenteric and should be grouped under the classification enterocolitis haemorrhagica. The great variability in the appearance of the usual signs and symptoms of these dysenteric infections is more important from a prognostic point of view than the local pathologic changes; it is a common occurrence, for example, to find a child dying of acute toxemia without manifesting any of the usual phenomena of dysentery. Autopsies alone can clear up the diagnosis in these cases. The onset in these invasions is brusque, with a rapid appearance of torpor, dehydration and profound circulatory disturbances; in a few hours acidosis develops, and the picture characterized by Finkelstein as decomposition is present. Treatment is carried out on lines generally accepted by the medical profession.

AMESSE, Denver.

TETANUS OF UMBILICAL ORIGIN IN ALGERIA. H. JAHIER, Bull. Soc. d'obst. et de gynéc. **22**:160 (Feb.) 1933.

Three fatal cases of tetanus are reported, two in native children and one in the child of a Spanish gardener. In the latter case the cord was severed with the same scissors used for cutting the stalks of flowers and vegetables. The two other patients were delivered on the ground by the soiled hands of natives.

GLASER, Rochester, N. Y.

CONGENITAL MALARIA. H. JAHIER, Bull. Soc. d'obst. et de gynéc. **22**:162 (Feb.) 1933.

The mother of an infant had a recurrent attack of malaria during the last days of pregnancy. Just previous to delivery numerous malarial organisms of the benign tertian type were demonstrated in her blood smears. The infant was delivered by forceps. No hematozoa were demonstrated in the cord blood or in the blood of the infant. The child was isolated from her mother and protected from mosquitoes; she progressed normally until the age of 15 days. Fever then developed, and enlargement of the spleen and liver was noted. Benign tertian organisms were demonstrated in the blood stream. This is the third case of this nature that the author has seen. He believes that the placenta, which may normally be impervious to the passage of malarial organisms, may become pervious during its separation in the course of labor, and thus a small amount of infected maternal blood may reach the infant's circulation. It requires about fifteen days for clinical symptoms to develop, and since most infants are discharged from the hospital at the age of from 10 to 12 days, congenital malaria is seldom seen in hospital

practice. In the discussion a case is mentioned in which a woman was delivered during an attack of malaria. Hematozoa were demonstrated in the placental blood and in the blood of the infant at the time of birth. At the age of 17 days the infant had an attack of malaria.

GLASER, Rochester, N. Y.

METABOLISM DURING THE COURSE OF ACUTE INFECTIONS. A. GARIBBO, Arch. ital. di pediat. e puericult. **1**:373 (Dec.) 1932.

The author presents detailed reports of the clinical courses of various acute infections in forty children. In general, determinations of the basal metabolic rate were similar in lobar pneumonia, bronchopneumonia, bronchitis, cerebrospinal meningitis, measles, scarlet fever, diphtheria, erysipelas and acute tonsillitis. During the febrile stage the basal metabolic rate was elevated, frequently to plus 20; but as soon as the temperature fell to normal the readings fell to negative levels, often as low as minus 20. The longer and more severe the acute stage, the lower the metabolism fell during convalescence, as a rule. In two fatal cases, one of lobar pneumonia, the other of capillary bronchitis, the basal rate fell to negative levels in the terminal stage, although the temperature and pulse rate were high. In one child, in whom postdiphtheritic paralysis developed, the readings had been negative throughout the course. In two babies with acute intestinal disturbances the readings had been negative throughout the illness.

DOOLEY, Kent, Conn.

STREPTOCOCCEMIA IN INFANCY: REPORT OF A CASE OF DENTAL ORIGIN. A. FILZI, Clin. Pediat. **15**:431 (June) 1933.

A fatal case of streptococcic septicemia is reported in a boy aged 10 years. The focus of infection was easily established in a carious tooth. The clinical course was fulminating, and in spite of heroic therapeutic efforts death ensued within two days. The author adds a comprehensive review of this subject as presented in the European literature.

SIGNORELLI, New Orleans.

INTRADERMAL VACCINATION AGAINST SMALLPOX. D. TIBONE, Prat. pediat. **11**:99 (March) 1933.

From a study of vaccination of 162 infants, the author concludes that the intradermal technic is the most satisfactory. The seventh month is the optimum age for vaccination. Of the infants studied, 64 per cent gained weight; in 22 per cent weight remained stationary, and 14 per cent lost weight during the period of reaction. Fever above 38 C. (100.4 F.) occurred in only 4 per cent. Digestive disturbances occurred in 4 per cent, a much lower percentage than in babies vaccinated by scarification.

DOOLEY, Kent, Conn.

DIPHTHERIA BACILLI AND DIPHTHEROID BACILLI IN THE NOSE OF THE INFANT. D. MOGGI, Riv. di clin. pediat. **31**:413 (April) 1933.

Nasal cultures of 103 infants showed diphtheria bacilli (Corynebacterium diphtheriae) in 1 case, Hoffmann's pseudodiphtheria bacilli (Corynebacterium commune) in 53 cases and other diphtheroid bacilli (Corynebacterium cutis) in 9 cases. Virulence tests on guinea-pigs are necessary for certain differentiation between C. diphtheriae and C. cutis.

HIGGINS, Boston.

PATHOGENESIS OF DIPHTHERITIC PARALYSIS: II. PHOSPHOLIPOIDS OF THE BRAIN AND DIPHTHERITIC TOXIN. C. COCCHI, Riv. di clin. pediat. **31**:513 (May) 1933.

The method of Whitehorn was used to determine the phospholipoids. Diphtheria toxin was added to an alcohol-ether extract of brain. The phospholipoid

content was found to be less than in a control experiment in which only physiologic solution of sodium chloride was added.

In a second experiment the toxin was added to dried guinea-pig brain, and the lipoids were then extracted with alcohol and ether. Again the phospholipoids were found to be less in the material treated with the diphtheria toxin than in the control material. Both the acetone-soluble phospholipoids and the nonacetone-soluble phospholipoids were found to be diminished.

Diphtheria toxin seems to cause a diminution in the phospholipoids by causing the building up of a more complex molecule. These observations regarding the diminution of the phospholipoids of the blood in postdiphtheritic paralysis fit in with others previously reported.

The author mixed 0.2 cc. (one fiftieth of the minimum lethal dose) of diphtheria toxin with 0.2 cc. of an ether solution containing 0.01 Gm. of lecithin. A mixture of the toxin and ether served as a control. After the preparation had stood for eighteen hours, the ether was evaporated and the mixtures were given intradermally to a guinea-pig. No reaction occurred after forty-eight hours at the site of the injection of the toxin and lecithin, while a marked reaction appeared where the control solution was injected.

The author was not able, however, to prevent death in guinea-pigs which were given mixtures of two and a half minimal doses of diphtheria toxin and as much as 0.01 Gm. of lecithin.

HIGIGNS, Boston.

SIGNIFICANCE OF THE PHENOMENON OF SCHULTZ-CHARLTON IN DEMONSTRATING IMMUNITY. L. BIDOLI, Riv. di clin. pediat. **31**:552 (May) 1933.

Four different commercial preparations of scarlet fever antitoxin were used in testing the Schultz-Charlton reaction in thirty-two children with scarlet fever eruptions; at least two of the serums were used in each case, and in many cases all four serums were used. In all cases at least one of the serums gave the blanching test. One serum gave the blanching test in 100 per cent of the cases in which it was tried; one, in 94 per cent; one, in 93 per cent, and one, in 77 per cent.

Tests with four different antistreptococcus serums (not antiscarlatinal) were carried out on twenty children with scarlet fever. With one serum, blanching occurred in 60 per cent of the patients observed; with two serums blanching occurred in one patient (5 per cent), and with the fourth serum no blanching was observed.

The serums of fifteen children in whom the Dick test had given positive results were used for the Schultz-Charlton test in two, three or four cases of scarlet fever. Two serums caused blanching consistently; three caused doubtful, slight or inconsistent blanching; the tests with the other ten serums gave negative results.

Similarly, the serums of fifteen children in whom the Dick test had given negative results were tried. Each serum caused blanching in at least two instances; with three of the serums the test was negative in one instance.

The Schultz-Charlton test demonstrates the fact that the serum used has antitoxic properties for the toxin of scarlet fever. It is more exact than the Dick test, as the Dick toxin may show anaphylactic reactions.

HIGGINS, Boston.

ANTIDIPHTHERITIC VACCINATION WITH THE ANATOXIN OF RAMON. V. PINTOZZI, Riv. di clin. pediat. **31**:678 (June) 1933.

This paper contains observations and deductions drawn from experience with the Schick test and with immunization with Ramon's anatoxin in the pediatric clinic and other institutions in Florence.

As a routine, three doses of anatoxin were given, 0.5 cc., 1 cc. and 1.5 cc., with an interval of twenty days between the first and second doses and of ten days between the second and third doses.

Before the Schick test is repeated, one should wait until twenty-eight days after the immunization is complete. Previous to that time, a positive Schick test may be obtained, whereas later it will be negative.

Of 618 children immunized, 573, or 94 per cent, showed a negative reaction to the Schick test sixty days later. The percentages of successful immunizations in the different age groups are as follows:

Age	Per Cent
Birth to 2 years	100
2 to 4 years	95
4 to 8 years	97
8 to 12 years	92
12 to 16 years	91
Over 16 years	81

If the Schick test was positive after three injections, a fourth injection was given, and a negative Schick test frequently resulted.

The heavier the subjects, the lower was the percentage of negative Schick tests after the immunization.

A positive tuberculin test did not affect the ability for immunization by anatoxin.

Local reactions may follow one or all of the injections, but they were found in only 1.5 per cent of the cases after the first injection, in 2.6 per cent after the second and in 1.6 per cent after the third. General febrile reactions were observed in 3.9 per cent of the cases after the first injection, in 11.2 per cent after the second and in 10 per cent after the third. Most of the reactions, both local and general, were in the older children, indicating the advantage of early immunization.

HIGGINS, Boston.

MALARIA IN THE CHILD. P. NOBECOURT, Bol. Soc. cubana de pediat. **4**:213 (June) 1932.

This distinguished clinician reports the occurrence of malaria in two children, aged 12 and 10½ years, in both of whom the malarial plasmodium was introduced by transfusions of blood from a donor who had had malaria seven years previous to the transfusion.

Nobecourt points out the amazing fact that the plasmodium can have such longevity and persist in a host without causing unusual symptoms or disability. He emphasizes the importance of making a careful examination and obtaining the complete histories of donors of blood.

SCHLUTZ, Chicago.

PATHOLOGIC ANATOMY OF PERTUSSIS. EDUARDO BENNEWITZ DECHER, Rev. chilena de pediat. **3**:481 (Dec.) 1932.

The anatomicopathologic lesions of pertussis consist in a bronchopulmonary infiltration. This infiltration rapidly invades the endobronchial and interstitial peribronchial and perivascular spaces and is accompanied by variable exudation into the alveolar cavities. From a histopathologic standpoint, the process consists entirely of a catarrhal inflammation of the air passages. The roentgenographic findings parallel the histologic findings. This inflammatory process develops in the earliest stages of the disease. The prolonged duration of the disease is due to these processes.

SCHLUTZ, Chicago.

A CLINICAL CONTRIBUTION TO THE KNOWLEDGE OF GONORRHEA IN CHILDHOOD: III. ENDOSCOPIC EXAMINATION IN THE DIAGNOSIS OF GONORRHEA IN CHILDREN. L. VON DOBSZOY, Arch. f. Kinderh. **100**:37 (July 18) 1933.

The use of the endoscope causes no physical or psychic harm to children with gonorrhea and in many cases is indispensable in establishing the correct diagnosis

and treatment. In the author's clinic a routine examination with the endoscope is made on every child with vulvovaginitis. Information obtained by endoscopic examination cannot be obtained by any other method.

LEMASTER, Evanston, Ill.

PREVENTION OF CONTAGIOUS DISEASES IN CLOSED INSTITUTIONS FOR CHILDREN. ERICH NASSAU, Gesundhfürs. f. d. Kindesalt. **8**:46 (Feb.) 1933.

The author compares the percentage of contagious diseases in institutions where the children stay night and day for long periods, with the percentage found in institutions where the children remain only during the day. In both types of institutions the percentages of contagious diseases observed were about equal, but, whereas in the former the number of cross-infections was small, in the latter the disease spread rapidly through the institution. This is, of course, due to the difficulty of separating the children in institutions where they are not under control for twenty-four hours. The diseases which have caused most trouble are chickenpox, whooping cough, measles and German measles.

In a closed institution Nassau was able to reduce the percentage of infection to a low figure by the strict isolation of newly admitted children. These were kept in a separate portion of the house for at least two, and usually three, weeks. Each ward contained from twelve to twenty children, and their activities were completely separated from those of the children in the other wards. Nassau adopted the practice of dressing them in a different fashion so as to be sure that no contact could occur. He believes that the same good results could be obtained in semiclosed institutions if the children were organized into small groups, each containing about fifteen. He admits that this would require a larger initial outlay of capital, but it would decrease the percentage of contagious disease among the younger groups.

REICHLE, Cleveland.

RECURRENCES IN SCARLET FEVER. ECKART HERRE, Monatschr. f. Kinderh. **58**:293, 1933.

The writer uses a case report as a basis for a review of the subject of recurrences of scarlet fever. Recurrences unquestionably exist, though they are rare. They are of two types, early and late. The early type occurs usually between the third and the sixth week after the original onset and is presumably due either to a reinfection by the original organism or to an entirely new infection. Allergy may play a rôle. The attack is usually mild and of short duration.

The late recurrence develops two years or more after the attack. This is due to a definite new infection following the wearing off of the immunity.

GERSTLEY, Chicago.

VACCINATION AND DIPHTHERIA OF THE SKIN IN SIBLINGS. HANS SKALETZ, Monatschr. f. Kinderh. **58**:446 (Aug.) 1933.

This is a report, with photographs, of complications following vaccination. A 12 year old girl was vaccinated. The infection was transmitted to the 5 year old brother, who had severe eczema. Diphtheria was implanted on the generalized vaccinia. The vaccinia and diphtheria were then carried to a 4 year old brother. Photographs show the involvement of the mouth, eyes, tongue, scrotum and penis.

GERSTLEY, Chicago.

IMPORTANCE OF SUBTHRESHOLD INFECTION IN THE EPIDEMIOLOGY OF INFANTILE PARALYSIS. O. ULLRICH, Ztschr. f. Kinderforsch. **41**:357 (May 17) 1933.

Pfaundler developed the conception of subthreshold infection several years ago. By this he meant that persons may become infected with minimal doses of some infectious agent or may show minimal forms of reaction to a normal dosage and

yet acquire immunity to the particular disease. In this way he attempted to explain the immunity to diphtheria and scarlet fever which develops in a population of which only a relatively small percentage contract the clinical disease. Certain diseases, such as measles, apparently never cause subthreshold immunity; an infection always leads to clinical manifestations.

Pfaundler recently examined poliomyelitis in the light of the same conception. His statistics seem to show the following peculiarities. Epidemics which affected certain localities seemed to spare these areas subsequently, although neighboring districts were attacked. This appears to show that the entire population of the spared district was immunized during the first epidemic, not by the clinical disease but by a subthreshold infection. In 1905 an epidemic appeared in the larger cities and along paths of communication. In the years from 1911 to 1913 the distribution of the disease, on the contrary, was greatest in the country, and the cities had the lowest morbidity. In other words, the cities had been immunized by the first epidemic. Another proof is seen in the distribution of the disease according to age. In the country the morbidity was higher in every age group, but the differences increased with increasing age; that is, in the cities children were chiefly affected, whereas in the country younger persons up to the age of 20 were frequently affected. Pfaundler explains that this was due to the subthreshold immunization of children in the city, which the country child had escaped. Again, it is noteworthy that in the years from 1911 to 1913 the children of the lower social classes were affected to a less degree than those of the wealthier population. He also shows that in parts of the world which are removed from commerce the native population has been affected by the disease to a high degree. In the equatorial island of Nauru the incidence was 38 per cent whereas only 2.5 per cent of the Europeans living in the same island were affected. He calls attention to the fact that animals which have apparently escaped the disease after having been inoculated with the virus may nevertheless show immunity.

REICHLE, Cleveland.

REPORT OF FOUR CASES OF HYDROPHOBIA. ZOFIA LEJBACHOWNA, Pedjatria polska **13**:29, 1933.

A peculiarity in three cases of hydrophobia was that the patients had been vaccinated against the disease. The time of onset after vaccination was from eight weeks to eighteen months. Some investigators have reported onset after five years. All of the patients died. The most characteristic symptoms in all of these cases were difficulty in deglutition and hydrophobia. When a current of air was directed on the eyeball, spasm of the muscles of the wall of the thorax resulted.

KRUPINSKI, Chicago.

Chronic Infections

DISPENSARY EXAMINATION VERSUS SCHOOL EXAMINATION IN DISCOVERING TUBERCULOSIS IN CHILDREN. EZRA BRIDGE and A. M. STOKES, Am. Rev. Tuberc. **28**:522 (Oct.) 1933.

The incidence of tuberculosis was four times as great among contacts and children not up to par in the group seen in dispensaries than among the children of the rural schools of New York State. Ten times as many cases of diffuse tuberculosis of the childhood type and of tuberculosis of the adult type were found in the group in dispensaries (contacts and children presenting symptoms of ill health) than were found in the group examined in schools.

In each group the diagnosis depended principally on the roentgenogram of the chest, which the authors consider the best means of demonstrating tuberculosis of the lungs in children. The criteria on which they based their findings were as follows: Deposits of calcium in the parenchyma of the lungs, in the regional lymph nodes or in both are pathognomonic of healed, healing or active tuber-

culosis. Infiltrations or localized areas of fibrosis are always considered suspicious and definitely so if they are seen at or near the periphery of the lung, with the involvement of regional lymph nodes. Calcification of cervical nodes and pleurisy with effusion are tuberculous. Diffuse abnormalities among the bronchogenic structures are probably nontuberculous.

EUGENE SMITH, Ogden, Utah.

THE INFLUENCE OF FOODSTUFFS UPON THE RESPIRATORY METABOLISM AND GROWTH OF HUMAN TUBERCLE BACILLI. R. O. LOEBEL, E. SHORR and H. B. RICHARDSON, J. Bact. **26**:139 (Aug.) 1933.

Keeping in mind that in any tuberculous lesion the bacilli must obtain energy for life and growth and that the processes involved and their significance for the progress or the arrest of a lesion can be investigated by studying, first, the metabolic characteristics of the bacteria and, second, the environment to which they are exposed, the authors carried out experiments which are given in detail in the paper. They found that bacilli of the H 37 strain consume oxygen at a rate which is comparable to that of mammalian cells.

One of the foodstuffs which causes the highest consumption of oxygen is glycerol. However, for purposes of oxidation this can be replaced by a number of substances. These are sodium lactate, the sodium salts of the higher fatty acids, and diluted blood serum or caseous material. Lecithin, milk and serum fat fall in the same category. Smaller effects are observed with dextrose and glycogen.

For respiration, it is not necessary that the substances mentioned should be present in the concentrations required for abundant growth. Both lactate and dextrose are effective in the concentrations at which they occur normally in the blood. According to the authors, these observations explain how it may be possible for the tubercle bacillus to obtain energy from the circulating blood in the body at concentrations of various foodstuffs which in culture mediums may be unable to support rich growths. Concerning the rôle of white blood cells in supplying the bacteria with foodstuff, the authors suggest that the monocytes might furnish lactate and glycogen more readily to the organisms than to the circulating blood.

A study of caseous material, which contains several ingredients each of which is capable of supporting a high level of respiration in bacilli of the H 37 strain, reveals evidence that there is an adequate food supply and that there is not any toxic effect on the respiration for several hours.

STOESSER, Minneapolis.

THE INFLUENCE OF ADVERSE CONDITIONS UPON THE RESPIRATORY METABOLISM AND GROWTH OF HUMAN TUBERCLE BACILLI. R. O. LOEBEL, E. SHORR and H. B. RICHARDSON, J. Bact. **26**:167 (Aug.) 1933.

In a previous paper the authors made a survey of the metabolic conditions which favor the survival and development of the tubercle bacillus, and in the present study they examine the environmental features which interfere with its survival and development.

It was found that the organism reduces its metabolism to a very low level after a few days of starvation. The addition of adequate foodstuff, even after many days, restores the respiration to its original level. At the same time its capacity for growth does not suffer destruction. This ability to reduce respiration to a low level with retention of the respiratory and proliferative capacity is not a general property of bacteria. It is apparently one of the factors contributing to the hardiness of the tubercle bacillus.

The question of intracellular or extracellular destruction of bacilli of the H 37 strain by acid or base in the body is discussed in some detail.

An anaerobic exposure of bacilli of the H 37 strain on Long's medium or under nonnutrient conditions leads to complete destruction of both the respiratory and the proliferative capacity in a few days.

The center of the tubercle is considered by the authors to have a complete lack of oxygen when its radius is between 0.075 and 0.35 mm. Under these circum-

stances the monocytes and bacilli in the central area would have to depend on some anaerobic mechanism for obtaining energy in order to survive. The monocytes can produce lactic acid to provide the necessary energy and might therefore survive. The tubercle bacilli, on the other hand, are unable to regain respiratory or proliferative capacity after anaerobiosis and therefore might not survive. The possibility exists, therefore, that the tubercle can bring about a cessation of growth or even an eradication of tubercle bacilli by means of this mechanism.

The paper is rather difficult to abstract in a brief way and therefore should be consulted for details.

STOESSER, Minneapolis.

TUBERCULOSIS OF THE FLAT BONES OF THE VAULT OF THE SKULL. DAVID C. STRAUS, Surg. Gynec. & Obst. **57**:384 (Sept.) 1933.

The report is based on a study of 220 cases, beginning with 2 cases reported by Ried of Erlangen in 1842. Straus adds a detailed report of 3 cases which he observed. One half the cases occurred before the tenth year of age and three fourths before the twentieth year. Of 184 cases, only 5 occurred in the first year of age. Local trauma may be an etiologic factor explaining the greater incidence of the condition in males.

The infection is usually hematogenous, originating in an antecedent lesion in the pleural or cervical lymph glands. Rarely, the cranial bones become involved through primary infection by way of the nasal mucous membrane (Reber). The hematogenous infection typically localizes first in the vascular cancellous bone of the diploe, in infants rarely beginning in the periosteum and more rarely in the dura. The frontal and parietal bones are most often attacked.

The disease may be (1) circumscribed perforating or (2) diffuse progressive in type. In type 1 the focus in the diploe characteristically exhibits greater destruction of the internal table, in distinction from syphilitic osteitis, which attacks chiefly the external table. Type 2 tends to spread and infiltrate progressively, producing tuberculous granulations between the internal table and the dura in the form of external pachymeningitis. Lesions in soft parts within and without the skull are associated, tuberculous meningitis occurring infrequently, however, because of the protection afforded by the thickened dura.

Symptoms are not noticeable until the local swelling from a subperiosteal abscess makes its appearance, calling for differentiation between a cold abscess and a cephalhematoma. In some cases headache and signs of cortical irritation have been noted.

Diagnosis is confirmed by x-ray picture, the Mantoux test and inoculation of guinea-pigs with material from the abscess. (Contributing evidence is afforded by x-ray pictures of the pathologic change in the lungs and ribs in the author's personal cases.) In differential diagnosis of the condition one must exclude gumma, acute and chronic osteomyelitis of the skull, osteoma, perforating malignant tumor of the dura, cephalhematoma, sebaceous cyst, lipoma, angioma, osteitis fibrosa cystica, actinomycosis and hydatid cyst. The prognosis is best in primary cases and in those involving the external table alone.

Treatment calls for radical excision of the diseased tissue. Eighty-seven operations have been recorded as resulting in 60 complete cures, 18 deaths and 9 incomplete cures, i. e., with fistulas.

The author's own appended case reports and illustrations are essential aids in the full presentation of the subject.

GRAVES, New York.

TUBERCULOSIS IN AN UNUSUAL SITUATION. W. C. WILSON, Tr. Edinburgh Med.-Chir. Soc., 1933, p. 168; in Edinburgh M. J., September 1933.

A 7 year old boy had limped and been stiff in one leg for two months; an abscess appeared in the buttocks, coming from disease and destruction of bone at the junction of the ischium and pubis. The abscess cavity was old, as evidenced by calcification of its walls. After five months of treatment healing is proceeding

in the ischium, but the disease is advancing up the pubic bone, with some rarefaction of the femur but without involvement of the joint. Immobilization in a plaster cast has been the treatment.

NEFF, Kansas City, Mo.

THE ERADICATION OF BOVINE TUBERCULOSIS. L. JORDAN, Medical Research Council, Spec. Rep. Ser., no. 184, London, His Majesty's Stationery Office, 1933.

This report is based on the results of a large scale attempt to eradicate bovine tuberculosis from an area of farming country near Mauchline, Ayrshire. The dairy farmers were offered free expert advice and free tuberculin testing of their cows on the understanding that they would attempt to eradicate tuberculosis from their herds by isolation. The experiment was carried out for a period of three years. Of the thirty herds participating, twenty-eight made substantial progress; twenty were free from infection at the end of the experiment (as compared with eight at the beginning), while eight others showed a marked reduction in the number of animals reacting to the tests. In all these herds the stock showed a general improvement, resulting in increased valuation and increased demand, while the cost incurred by the owners in eradicating the disease was small and was more than offset by the increased value of the stock. The report gives a good example of the way in which an investigation in the field carried out under scientific control can eradicate tuberculosis from heavily infected herds by providing free tuberculin testing and free expert advice.

LEMASTER, Evanston, Ill.

TUBERCULOUS INFECTION IN MILK: A REPORT BY THE DEPARTMENT OF HEALTH FOR SCOTLAND. Medical Research Council, Spec. Rep. Ser., no. 189, London, His Majesty's Stationery Office, 1933.

The chief object of this inquiry was to ascertain with exactitude and by uniform methods of examination the extent of infection with tubercle bacilli in various types of milk consigned to and consumed in the four principal cities of Scotland. Ten per cent of the samples of raw milk in churns were infected with tubercle bacilli. The degree of infection increased with bulking, so that tubercle bacilli were found in one third of the samples taken from tanks containing 500 gallons (1,893 liters) of milk. The incidence of tubercle bacilli in milk treated by heat was quite low, 2.8 per cent in milk treated by the holding method and 8.2 in milk treated by the flash method. Only one positive case was found in over seven hundred tests made of certified and grade A milk. The necessity of a standard method of examination for comparison between different areas is strongly emphasized.

LEMASTER, Evanston, Ill.

POLYMORPHOUS HEREDITARY SYPHILITIC LESIONS OF THE EYE OBSERVED IN THREE BROTHERS. J. ROLLET, Ann. d'ocul. **170**:542 (June) 1933.

Hereditary syphilitic lesions of the eye were noted in three brothers; the two older ones had interstitial keratitis; the second child also had unusual peripapillary lesions, which were observed likewise, in the third. In addition, the third brother had Argyll Robertson pupils.

BERENS, New York. [ARCH. NEUROL. & PSYCHIAT.]

RATE OF RED CELL SEDIMENTATION IN CASES OF TUBERCULOSIS IN CHILDREN. R. LIÈGE, GRODNITZKY and A. HERR, Bull. Soc. de pédiat. de Paris **30**:93 (Feb. 16) 1932.

A modification of Linzenmeyer's microsedimentation test was used. Twenty-six children with tuberculosis were studied. An increased rate was found in almost all of the cases of glandular or pulmonary tuberculosis, and in general the more severe the disease the more marked was the increase. However, two girls of

approximately the same age with caseous pulmonary tuberculosis had dissimilar rates. Usually the rate increased with exacerbation of the disease and decreased gradually with subsidence of the clinical signs and symptoms. It was not reliable in cases of tuberculous disease of the serous membranes. Children with pleurisy generally had elevated rates, whereas two patients with tuberculous pericarditis had repeatedly low rates—one recovered and the other died. In seven cases of tuberculous meningitis the rate was not increased to the same extent as in cases of other forms of tuberculosis.

BENJAMIN, Montreal, Canada.

SEVERE KALA-AZAR IN A CHILD OF TWO YEARS; LATENT LEISHMANIASIS IN A DOG IN CONTACT WITH THE CHILD. PAUL GIRAUD and JEAN RAYBAUD, Bull. Soc. de pédiat. de Paris **30**:574 (Nov. 15) 1932.

A girl, 23 months old, had septic fever, lost weight and color, and showed gradual enlargement of the abdomen. There was marked enlargement of the spleen; the liver was not palpable; the superficial lymph nodes were about the size of peas. The blood showed a low red cell count, leukopenia and marked lymphocytosis. The formol-gel test was positive. Fluid obtained on splenic puncture contained Leishmania. The child's condition improved, but there were several remissions, and she died about nine months after the first febrile attack. A dog which had been in contact with the child was examined. The findings in the animal's blood were similar to those found in the child, and the formol-gel test was positive. Slides made from the material obtained by puncture of the liver contained two questionable parasites. When the animal was killed, the bone marrow showed numerous parasites identified as Leishmania, although the liver and spleen showed few and the lymph nodes none. The dog had been in good health, had no ulcers of the skin and was not infested with fleas.

BENJAMIN, Montreal, Canada.

LARGE CAVITY APPEARING IN AN INFANT AFTER VOMITING. M. ARMAND-DELILLE, LESTOCQUOY and GAVOIS, Bull. Soc. de pédiat. de Paris **30**:652 (Dec. 20) 1932.

On roentgenologic examination an infant, 6 months old, born of tuberculous parents, showed an egg-shaped density placed vertically in the right upper half of the chest. This corresponded with physical signs of consolidation in this area. Immediately after an artificial pneumothorax was induced the infant vomited a large amount of greenish-yellow pus and went into a state of collapse requiring artificial respiration. The chest then showed physical signs of a large pulmonary cavity, and the roentgenogram confirmed its presence. Pneumothorax was induced repeatedly and the cavity seemed to be reducing in size, but the infant died suddenly about two months after the first treatment. The reaction to tuberculin was strongly positive. The infant had not received B C G vaccine. The gastric contents after fasting showed no tubercle bacilli before the vomiting, but bacilli were demonstrated by gastric lavage after the vomiting. Smears made from the pus which was vomited showed no tubercle bacilli. At autopsy the diagnosis of a pulmonary cavity was confirmed, and tubercle bacilli were demonstrated in the caseous contents of enlarged trachebronchial lymph nodes. Apparently the lesion in the lung constituted the primary focus of infection in this case.

BENJAMIN, Montreal, Canada.

SEVERE GOLD INTOXICATION DESPITE SMALL DOSES: CUTANEOUS MANIFESTATIONS AND BLOOD CHANGES. M. ARMAND-DELILLE, GAVOIS and V. BAYLE, Bull. Soc. de pédiat. de Paris **30**:654 (Dec. 20) 1932.

A girl, 14 years old, who had pulmonary tuberculosis, was given injections of small doses of a preparation containing gold. Signs of intoxication developed,

chief of which were a digestive disturbance, a reddened throat, an urticarial cutaneous rash with some purpuric lesions, metrorrhagia and leukopenia with agranulocytosis. The patient was subject to an urticarial eruption of the skin after eating egg and fish, and it is thought that she had some sensitivity to gold salts. She received six injections of gold sodium thiosulphate totaling 0.70 cg. over a period of six weeks. Signs of intoxication appeared two months after the first injection.

BENJAMIN, Montreal, Canada.

CONGENITAL SYPHILIS IN A CHILD SHOWING REPEATED SIGNS OF ACTIVITY WHICH SUBSIDED RAPIDLY BUT NOT PERMANENTLY WITH SPECIFIC TREATMENT. M. LINOSSIER-ARDOIN, Bull. Soc. de pédiat. de Paris **30**:674 (Dec. 20) 1932.

A girl, 8½ years old, had mucocutaneous lesions at the age of 20 days, an ocular lesion at 2 years and multiple lesions of the bones at 4 years; all of these subsided promptly under antisyphilitic treatment and remained quiescent for varying periods. The child showed some involvement of one eye, and the Wassermann reaction was strongly positive. It is emphasized that the treatment was inadequate. Although the clinical signs cleared up each time when some antisyphilitic therapy was administered, the cure was only apparent and fleeting. Before the child is considered cured treatment should be persisted in for at least two years, and the Wassermann reaction should become negative and remain negative when repeatedly checked at frequent intervals. At the return of even the slightest positive reaction treatment should be resorted to at once and continued until the reaction turns negative and remains so when repeatedly checked. The clearing up of the clinical manifestations of syphilis is not to be used as a guide for the amount of treatment necessary.

BENJAMIN, Montreal, Canada.

CONGENITAL SYPHILIS. JEAN OLIVER, Progrès méd., July 29, 1933, p. 1354.

The fetus may be contaminated from the mother in any month of pregnancy. The usual way is from the placenta; certainly contaminations during birth are exceptional. The effect of treatment of the mother on the fetus is so variable that one cannot say with certainty that the child will show protection when born. Likewise, as to the time during pregnancy when the mother is infected, the effect on the child is variable. The entire subject may be summed up in saying that a syphilitic woman should be very carefully treated and examined before being allowed to marry, as she is likely to carry the disease in a latent stage. If it is not certain that the woman is free from syphilis, she should be actively treated during pregnancy. If there is any question of a mother having syphilis in a latent stage, and the prenatal treatment was inadequate, the infant should be treated regardless of an apparently normal physical condition.

SANFORD, Chicago.

CONGENITAL SYPHILIS OF THE BONES IN EARLY INFANCY. M. PEHU and A. POLICARD, Paidoterapia **12**:425 (Sept.) 1933.

The spirochete invades the skeleton of the fetus very quickly and attacks the bones of cartilaginous origin. The osseous lesions are symmetrical. The authors propose a division into five classes: (1) osteochondritis, (2) periostitis, (3) osseous rarefactions, (4) hypertrophy of the bones and (5) transverse bands on the metaphysis. Osteochondritis appears first in intra-uterine life and is the forerunner of periostitis. The bony rarefactions and hypertrophies are easily seen by x-ray picture. The transverse bands are present on the diaphysis just back of the epiphysis and are more easily seen in the long bones. The x-ray picture is of great value as an aid to diagnosis.

HERRON, Spokane, Wash.

FREQUENCY AND COURSE OF ESSENTIAL ENURESIS IN CHILDREN OF TUBERCULOUS PARENTS. A. DELARIA, Pediatria **42**:24 (Jan. 1) 1934.

Essential enuresis in children of tuberculous parents is reported in this article as being more frequent in males, reaching a total percentage of 19.4. The disorder occurs especially in slender or lymphatic children and is probably due to the particular anatomicobiochemical type of these patients.

SIGNORELLI, New Orleans.

FOCAL REACTIONS: I. THE PARAHILAR TRIANGULAR INFILTRATIONS OF SLUKA. P. FORNARA and L. GREPPI, Riv. di clin. pediat. **31**:1172 (Oct.) 1933.

Fornara and Greppi have observed four children with early tuberculosis showing by x-ray picture the triangular parahilar shadow described by Sluka in 1912. The triangle of Sluka has its base in the hilus of the lung and its apex in the axilla. The authors discuss its pathologic significance. It may represent the primary focus of tuberculosis of the hilus or an infiltration of the lungs emanating from diseased hilar glands or an interlobar pleurisy.

HIGGINS, Boston.

AUROTHERAPY IN SCROFULOUS OPHTHALMIAS. PEDRO MATA, Arch. de oftal. hispano-am. **33**:9 (Jan.) 1933.

After a detailed review of different points of view of the relation of scrofula and tuberculosis, from 1850 to the present, Mata concludes in favor of an identical pathogenesis, the difference in clinical manifestations arising from differences in resistance to the tubercle bacillus, which may in consequence present morphologic and other variations.

He has employed the different therapeutic measures based on this point of view—tuberculin, hygienic and dietetic treatments and Spengler's immune bodies—with more or less similar nonsatisfactory results. For the last three years he has been using gold salts. He reviews the action of these, with the different explanations offered, leaning to Mollard's, which attributes it to modification of the "terrain" by the combined action of gold and sulphur contained in the three preparations employed, which were all gold thio-organic compounds.

FINLAY. [ARCH. OPHTH.]

MORBIDITY OF TUBERCULOSIS AMONG PRESCHOOL AND SCHOOL CHILDREN IN THE INDUSTRIAL AND RURAL DISTRICTS. PERETTI, Gesundhfürs. f. d. Kindesalt. **8**:184 (Aug.) 1933.

From a study of the morbidity of tuberculosis in children of preschool and school age in the industrial and rural parts of Germany, the author concludes that the morbidity of tuberculosis has decreased in proportion to the mortality, thus illustrating the importance of the elimination of contacts.

REICHLE, Cleveland.

OSTEITIS TUBERCULOSA MULTIPLEX CYSTICA, WITH SARCOID AND INVOLVEMENT OF THE HILAR NODES. WILHELM BAYER, Jahrb. f. Kinderh. **138**:31 (Jan.) 1933.

A case was observed for a period of four years. At no time did the results of tuberculin tests or animal inoculations point to tuberculosis.

CLAUSEN, Rochester, N. Y.

THE TUBERCULIN INDEX OF CHINESE SCHOOL CHILDREN. J. H. DE HAAS, K. T. SIOE and T. K. HONG, Geneesk. tijdschr. v. Nederl.-Indië **73**:934 (July 18) 1933.

In connection with investigation of the reaction to tuberculin among Chinese babies and infants in Batavia, De Haas, Sioe and Hong examined the Pirquet

reactions in 2,394 Chinese school children in Batavia, which children can be regarded as being an average of Chinese school children. Forty per cent of the children entering school for the first time had a positive Pirquet reaction; of the children from 6 to 9 years of age, 70 per cent, and of those from 10 to 14 years of age 80 per cent had a positive reaction. These figures are not exact but are the approximate minimal percentages. Before Chinese children enter school the degree of infection among them is as high (from 40 to 50 per cent) as among European and American children leaving school. The tuberculin index of Chinese school children is much higher than that of children of tuberculous surroundings in the Hague or in Amsterdam (The Netherlands) and is as high as it was from fifteen to twenty-five years ago among the most unfavorable circumstances.

VAN CREVELD, Amsterdam, the Netherlands.

TUBERCULOUS MENINGITIS WITH AN ABNORMAL CLINICAL COURSE. L. J. C. THIANGE, Maandschr. v. kindergeneesk. **2**:424 (June) 1933.

A child, aged 1 year, showed the typical picture of acute severe encephalitis. The Pirquet reaction was weakly positive. At autopsy a tuberculous process was found, with localization at the convexity of the brain and penetrations into the brain tissue.

VAN CREVELD, Amsterdam, the Netherlands.

Internal Diseases

ROENTGEN TREATMENT OF AGRANULOCYTOSIS: REPORT OF TWO CASES WITH RECOVERY. LESLIE T. GAGER and ALMA JANE SPEER, Am. J. Roentgenol. **27**:40 (Jan.) 1932.

The authors review the literature and add 2 cases which they report in detail. In 13 of 15 cases which were uncomplicated, Friedmann and Elkeles reported recovery under the stimulating influence of roentgen radiation on the long bones, although they make it clear that treatment is hopeless when secondary general sepsis or pneumonia supervenes (23 patients died, while 5 others died within thirty-six hours after the first irradiation). Taussig analyzed 340 cases of agranulocytosis—with a mortality of 79 per cent—and showed a death rate of 53 per cent in the group of 80 patients treated with irradiation of the long bones. By contrast, of 49 patients treated with transfusion, 69 per cent died; of 31 given neoarsphenamine, 77 per cent died, and the mortality was 75 per cent among 172 patients who received other treatment. It is thought that this is a demonstration of the specific value of roentgen radiation in stimulating the production of granulocytes and of the vital importance of these cells to the body as a whole.

STULIK, Chicago.

URINARY PROTEOSE: ALLERGIC DERMATOSES AND THE ECZEMA-ASTHMA-HAY FEVER COMPLEX. FRANK E. CORMIA, Arch. Dermat. & Syph. **27**:745 (May) 1933.

The author discusses the use of urinary proteose in the treatment of allergic dermatoses and in the cutaneous sensitivity tests in allergic patients. Urinary proteose (which is believed to be a complex, chemically impure protein substance) is found in normal persons; it is found in larger amounts in persons with eczema, asthma, hay fever and urticaria. The author does not believe in the specificity of the intradermal reactions with this substance and he cannot report improvement in any of eight allergic patients treated with intradermal injections of their own urinary proteose.

EKERMEYER, Iowa City.

HYPERPARATHYROIDISM (RECKLINGHAUSEN'S DISEASE OF BONE). HENRY L. JAFFE, Arch. Path. **16**:63 (July) 1933.

The status of present knowledge concerning generalized osteitis fibrosa cystica is thoroughly discussed. The first report by von Recklinghausen and later observations by other men are reviewed. The author presents a complete description of the pathologic picture found in this disease and discusses the extensive amount of experimental work performed in this field. The bibliography contains 109 references to the literature dealing with this condition.

LEMASTER, Evanston, Ill.

ENTEROSPASM SECONDARY TO UPPER RESPIRATORY INFECTION IN CHILDHOOD. S. E. PASETTE, Arch. Pediat. **50**:279 (April) 1933.

Attention is again called to the frequent occurrence of abdominal pain associated with infections of the upper respiratory tract. Three cases are presented in which abdominal pain is the outstanding symptom. It is pointed out that spasm of the bowel may precede the clinical manifestation of infection by several days, and that differentiation from other more serious abdominal conditions is occasionally difficult.

WADDELL, JR., University, Va.

GONORRHEA IN FEMALE CHILDREN, WITH SPECIAL REFERENCE TO TREATMENT. E. W. TITUS and BERNARD NOTES, Arch. Pediat. **50**:284 (April) 1933.

Attention is called to the frequency of gonorrhea in the early years of life, particularly in young girls, and the author believes that the establishment of special clinics is necessary to treat properly and prevent the spread of gonorrhea. The marked contrast of the disease in children as compared to that in adults is pointed out, and suggestions as to treatment are given. Attention is directed especially to the use of the cautery as a satisfactory and harmless instrument, if properly used.

WADDELL, JR., University, Va.

CELIAC DISEASE TREATED FROM THE STANDPOINT OF VITAMIN DEFICIENCY. C. V. RICE, Arch. Pediat. **50**:358 (May) 1933.

The author reports a case of apparent celiac disease which showed improvement as a result of therapy designed to correct vitamin deficiency. He believes that celiac disease is in all probability a nutritional disturbance, that it should be classified as such with beriberi, scurvy, pellagra, sprue, tetany and rickets and that it should be treated as a vitamin deficiency.

WADDELL, JR., University, Va.

SALYRGAN IN THE TREATMENT OF EDEMA ASSOCIATED WITH A MIXED TYPE OF NEPHRITIS. S. J. MCCLENDON, Arch. Pediat. **50**:363 (May) 1933.

The author reports a case of edema associated with a mixed type of nephritis; the patient was treated with mersalyl. The edema subsided promptly with this method of therapy, and there appeared to be no harmful effects from the use of the drug in mixed types of nephritis, even though the drug was administered over a prolonged period.

WADDELL, JR., University, Va.

PERICARDITIS SIMULATING AN ACUTE CONDITION OF THE ABDOMEN. JOSEPH GREENGARD and SAMUEL J. HOFFMAN, Arch. Surg. **26**:623 (April) 1933.

Acute abdominal pain at the onset of rheumatic fever is not uncommon. The character of the abdominal pain offers great difficulty in differentiating the condition from a surgical condition in the abdomen. The authors report three cases in children in whom the abdominal symptoms simulated an attack of

appendicitis. Operation in all three cases revealed a normal appendix, and rheumatic pericarditis subsequently developed. In two of these children there had been a definite history of preceding attacks of rheumatic fever, while in the third typical findings of mitral insufficiency were noted on physical examination. A careful history, with a search for rheumatic symptoms, will be an aid in differentiating the onset of acute rheumatic pericarditis from a surgical condition in the abdomen, but at times this question can be settled only by exploration of the abdomen.

KAISER, Rochester, N. Y.

TREATING THE PNEUMONIA PATIENT. ALEXANDER LAMBERT, Bull. New York. Acad. Med. **9**:355 (June) 1933.

The pneumococci producing pneumococcic pneumonia are divided into many types, each type separated from the other by a specific capsule; each type of pneumonia therefore demands a separate specific immunologic treatment. A discussion of the defense mechanism is submitted, the macrophages of the reticuloendothelial system in the respiratory apparatus being emphasized. The antibodies elaborated under the stimulus of a pneumococcic invasion in the lungs do not appear fully until the fifth day of the disease and at times not until the crisis has occurred. Specific treatment, whether by serum or by vaccine, is most helpful the first three days of the disease, before the exudate has had time to plug the capillaries. There is reason to believe that the action of the antibody consists in dissolving the polysaccharoid capsule of the pneumococcus, thereby preparing the germs for phagocytic invasion. The production of antibodies may be stimulated by the injection of a vaccine, and it seems that specific vaccine yields a specific antibody.

About thirty types of pneumococci have thus far been separated from the former type IV, and various antiserums have been produced. Type VII, which constitutes the flora in 5 per cent of the cases of lobar pneumonia, has recently yielded an effective serum.

The types for which there is no serum respond favorably to autogenous vaccines injected early in the disease, as is shown by the greater abundance of protective bodies in the blood. Though these bodies do not make their appearance earlier in persons infected with the types for which there is no serum than in the controls, the course of the disease is definitely more favorable. Vaccines are injected into the gluteus medius muscle, the back of the deltoid muscle on the shoulder or into the deltoid muscle itself. The injections are not accompanied by a rise in temperature.

Nonspecific treatment consists of measures affording all possible comfort, such as inhalations of oxygen, cardiac stimulation when indicated, giving of cough mixtures that tend to liquefy the sputum and allow the oxygen to reach the lungs, application of poultices to cover the pleural area in order to relieve the pain (pressure on the lower sixth intercostal nerve, especially the unprotected part which emerges from the vertebral foramen), administration of analgesics (codeine, salicylates, or both; morphine is contraindicated, as it paralyzes the action of the sympathetic suprarenal system), and hypnotics, care of the bowels and observation of the diet and the intake of fluid. Reduction of the temperature is not indicated except when it interferes with comfort; then sponges saturated with alcohol serve best. The patient should not be allowed to get out of bed until about a week after the temperature reaches a normal level.

JAHR, Omaha.

TRICHINOSIS RESULTS FROM EATING UNCOOKED SMOKED PORK, Health News (New York) **10**:33 (Feb. 27) 1933.

Trichinosis developed in two adults and four children in one family who ate uncooked pork. The meat had been packed in salt for three days and had then been smoked for three days. No deaths are reported.

AIKMAN, Rochester, N. Y.

FURTHER REPORT ON DUTCHESS COUNTY GASTROENTERITIS OUTBREAK. Health News (New York) **10**:37 (March 6) 1933.

One hundred and thirty-six cases of gastro-enteritis occurred in Dutchess county on Dec. 1, 2 and 3, 1932, from the eating of pies, cream puffs and éclairs made by one wholesale bakery. The poisoning was traced to cream custard filling and was thought to be due to some undetermined bacterial toxin, as no chemical poisons were found. While severe prostration and collapse developed in some cases, no deaths occurred.

AIKMAN, Rochester, N. Y.

PYURIA IN CHILDHOOD. J. A. BIGLER, Illinois M. J. **43**:345 (April) 1933.

Bigler believes that the urine of every sick child should be examined. The treatment of pyuria should be medical, unless symptoms or physical signs of some obstructive lesion are present. Complete urologic investigation becomes necessary in all cases of chronic or recurrent pyuria. Children with these conditions should not be followed or treated medically for months without the benefit of such an examination. When pyuria is present, the urine should be examined until it becomes negative. Check-up examinations at later dates should be made. The symptomatology accompanying pyuria in infants varies not only with the age of the patient but also in acute and chronic cases. There is usually an acute onset, with high fever and at times a convulsion. The temperature often reaches 105 F., fluctuates over a wide range and gradually subsides as the amount of pus in the urine decreases. A chill may accompany the high fever and, when present, is nearly always pathognomonic of pyuria, because it occurs so rarely in other diseases of childhood. Pallor, restlessness, irritability and crying are of frequent occurrence. These general symptoms may be those of any acute infection. Because of this, urinalysis is always imperative in any unexplained fever. In the older child, symptoms consist of dysuria, urgency and frequency in regard to urination and often tenderness over the bladder or kidney. When cystitis is present, the local symptoms are usually more severe than when only the upper part of the urinary tract is infected. In cases of chronic pyuria the fever, dysuria and other symptoms may be present only at irregular intervals, simulating recurrent acute pyuria. A suprapubic tumor, associated with dribbling and incontinence and disappearing after catheterization of the bladder, should make one suspect an obstruction of the neck of the bladder or a cord bladder. A tumor in one or both renal regions might indicate a polycystic kidney, a hydronephrotic kidney or a tumor of the kidney. Palpable enlarged tender kidneys may signify pyonephritis. A sausage-shaped tumor mass crossing the midline in the region of the umbilicus may be due to horseshoe-shaped kidneys with fusion at the lower poles. Hydronephrotic ureters are seldom palpable.

BARBOUR, Peoria, Ill.

ANEMIA OF INFANCY FROM MATERNAL IRON DEFICIENCY IN PREGNANCY. MAURICE B. STRAUSS, J. Clin. Investigation **12**:345 (March) 1933.

Within forty-eight hours after birth, examinations were made of the blood of fifteen infants whose mothers' blood contained less than 45 per cent of hemoglobin (hypochromic type of anemia) and of twelve infants whose mothers' blood contained more than 70 per cent of hemoglobin (100 per cent equals 15.6 Gm. of hemoglobin per hundred cubic centimeters). Infants born to women of the first group exhibited a normal blood picture at birth, but anemia of moderate to severe degree developed during the first year of life. For reasons that follow, it was concluded that this was due to deficient storage of iron by the fetus dependent on a deficient supply of the element in the mother, and that this form of anemia could be prevented or corrected by the administration of iron.

Three pregnant mothers suffering from severe hypochromic anemia, whose blood had a hemoglobin content of 35 per cent, were treated with 6 Gm. of iron and ammonium citrate daily during the last three months of pregnancy. At parturition the average hemoglobin content of the blood was 66 per cent. The blood of their

infants contained normal amounts of hemoglobin at birth and at the end of the first year. Moreover, six anemic infants who were given daily 1 Gm. of iron and ammonium citrate showed a prompt increase of hemoglobin in the blood.

GUEST, Cincinnati.

MORQUIO'S DISEASE: PRESENTATION OF TWO CASES. E. J. BARNETT, J. Pediat. **2**:651 (June) 1933.

In 1929, Morquio, of Uruguay, described an osseous dystrophy characterized by familial occurrence, dwarfism, changes in the epiphyses and, in many instances, absence of the heads of the femurs. Two cases of this condition occurring in sisters, aged 13 and 10 years, are reported, with photographs and roentgenograms. It can be seen from the photographs that the stature is short, the eyes are widely separated, the nose is depressed, the neck is short, the sternum is so pushed and bent forward that it appears as a "shelf on which the chin rests," the spine is kyphotic, the hips are flexed so that the child appears to crouch, the hands extend almost to the marked knock knees, the feet are kept apart, and the ends of the long bones are prominent.

LEMASTER, Evanston, Ill.

INCONTINENCE IN CHILDREN. BERT I. BEVERLY, J. Pediat. **2**:718 (June) 1933.

This report deals with 250 cases, mostly of nocturnal enuresis, which have been studied at the psychiatric clinic of the Children's Memorial Hospital and in private practice. While incontinence is a reason for bringing the patient to the physician, it is only one of many complaints which are easily elicited by securing a careful history. Nervousness is nearly always described. Other infantile habits, such as temper tantrums, thumb sucking, nail biting and infantile speech, are sometimes present. In other words, the incontinence is but one of a number of manifestations of a general behavior problem. Children stop the incontinence when they want to and when a sufficient motive has been furnished. Treatment consists of three phases: first, making the child responsible for himself; second, psychotherapy, and third, adjustment of environmental difficulties. It is more important to treat the underlying maladjustment than the symptom.

LEMASTER, Evanston, Ill.

POSTOPERATIVE MASSIVE ATELECTASIS OF THE LUNG. GEORGE B. BADER, J. Pediat. **2**:726 (June) 1933.

In a child, aged 12, massive collapse of the left lung developed a few days after appendectomy. Fever, dyspnea, cyanosis and impaired resonance over the left lung occurred, and the condition simulated postoperative pneumonia. Recovery was complete within fifty-seven days.

LEMASTER, Evanston, Ill.

THE RÔLE OF ERYTHROCYTE FRAGMENTATION IN THE GENESIS OF ANEMIA. THOMAS B. COOLEY and PEARL LEE, J. Pediat. **3**:55 (July) 1933.

Fragmentation of erythrocytes in various types of anemia was observed by means of fresh, moist blood preparations. Destruction of cells in this manner is distinct from hemolysis. The first case in which excessive fragmentation was studied showed evidence of hypoplasia of erythropoietic marrow plus greatly increased destruction by fragmentation of red cells and was apparently caused by the toxemia of focal infection. In three cases of erythroblastic anemia, more extreme fragmentation was seen than in any other cases, but increased erythropoiesis allowed the hemoglobin value and the red cell count to remain nearly stationary. In another case, in which the stained blood smears resembled a microcytic anemia, the erythrocytes were seen to divide in a peculiar manner to form the small, rounded microcytes. The authors feel that the study of moist blood films for fragmentation will prove to be of great value in determining the pathogenesis of anemias.

LEMASTER, Evanston, Ill.

STATUS THYMICOLYMPHATICUS WITH ORTHOSTATIC ALBUMINURIA. HARVEY G. BECK, M. Clin. North America **16**:1267 (March) 1933.

A boy, aged 15, complained of breathlessness on exertion, dizziness and a "tired feeling." His tonsils were removed when he was about 5 years of age. Following the operation he remained unconscious for about twenty hours. Subsequently he was treated for two years for some condition of the heart, and his activities were much restricted during this time. He continued to have frequent attacks of dizziness during which he lost consciousness, his lips became swollen and blue, profuse perspiration occurred, and he appeared to have difficulty in breathing. The attacks were precipitated by overexertion, excitement or emotion. Physical examination revealed delayed epiphyseal closure; late puberty; hypogenitalism; feminine features, with heterosexual distribution of pubic hair; a high-arched palate; an enteroptotic habitus; lumbar lordosis; hyperextensile joints, and lymphatic hyperplasia. The thymus gland was apparently of normal size. The systolic blood pressure was 8 mm. higher with the patient in the horizontal position than in the sitting position. With the patient sitting, the blood pressure was 42 mm. lower with the arm elevated than with the arm hanging down. Previous observations by the author have shown similar changes produced by posture in patients with vasomotor disturbances, including orthostatic albuminuria. Albumin was found in the urine of this patient, but this disappeared when he was kept in the recumbent position. The results of tests of renal function and the blood chemistry were within the physiologic limits. The patient's metabolic rate was minus 22, although his mental alertness and general symptoms did not suggest it.

The final diagnosis was orthostatic albuminuria associated with a constitutional abnormality of the thymicolymphatic type.

SMITH, Ogden, Utah.

MEDIASTINITIS. HERMAN J. MOERSCH and FRANK J. KENNEDY, M. Clin. North America **16**:1433 (May) 1933.

During the past five years, five cases of perforation of the esophagus as a result of ingestion of a foreign body, with development of periesophagitis, mediastinitis and pleuritis, have been seen at the Mayo Clinic. Two patients recovered. Much difference of opinion exists as to the proper treatment of these complications. Three possible methods of treatment are: (1) surgical drainage from the outside, (2) endoscopic drainage through the esophagus and (3) expectant treatment. Two cases are reported in this article:

CASE 1.—An infant, aged 3 months, two months previously had swallowed a safety-pin, which lodged in the upper part of the esophagus. It was removed by external esophagotomy without great difficulty, but the baby died six hours later. Postmortem examination revealed that the pin had been in the upper mediastinum in contact with the apex of the right lung. A small pulmonary abscess had formed at this point and was unroofed at the time of the operation. Death resulted from emphysema of the mediastinum.

CASE 2.—A child, aged 2 years, swallowed a nickel four days previous to admission. The coin had lodged in the upper part of the esophagus, at which point considerable necrotic tissue was seen. The coin was removed by external operation, but death occurred about four hours later. Postmortem examination showed a large opening which had permitted the coin to pass into the tissues of the neck and had allowed the escape of the esophageal contents into the mediastinum.

At this time it is impossible to formulate definite rules of procedure in these cases, but reports of cases of patients successfully or unsuccessfully treated may be of assistance to those confronted by such accidents.

SMITH, Ogden, Utah.

PNEUMONIA IN CHILDREN. LE GRAND KERR, M. J. & Rec. **137**:138 (Feb. 15) 1933.

The author gives the following criteria, which he considers absolutely essential to the diagnosis of lobar pneumonia in children: (1) sudden onset, with immediate

and continued high temperature; (2) early prostration; (3) increased respiration, with a disturbed ratio between pulse and respiration, and (4) exclusion of all other possible causes of the symptoms. He believes that pneumonia of short duration is overlooked, and that many cases of pneumonia are diagnosed as appendicitis in children. The danger in lobar pneumonia in children is not of cardiac collapse, but of gastric dilation, which is primarily due to toxemia. It is unusual for the heart to require active treatment during any stage of the disease. The symptoms of acute gastric dilation causing death may often be attributed to cardiac failure. Treatment must be prompt. Efficient lavage is the first stage in treatment; the stomach must then be kept empty for the next twelve hours, not even water being allowed. In bronchopneumonia there are the strain of high temperature on the heart and pulmonary stasis, which cause overdistention and, later, dilation of the heart. Often, however, death is due to rapid suffocation rather than to cardiac collapse. After the diagnosis is made, examination of the chest should be omitted until the crisis is near, but every opportunity should be taken to examine the abdomen.

WILLIAMSON, New Orleans.

HEMOCHROMATOSIS: A POSSIBLE DANGER OF COPPER THERAPY. JOSEPH R. DARNALL, Mil. Surgeon **73**:70 (Aug.) 1933.

It has been assumed that in copper therapy the mobilization of iron for hemoglobin is facilitated. If, also as a result of copper therapy, the elimination of iron is retarded and the deposition of iron in the tissues is augmented, copper may not be such a beneficial remedy as heretofore pictured. (Mallory, Parker and Nye produced hemochromatosis in animals by feeding copper, and their experiments were later confirmed by Hall and Butt.) Certainly the quantities of copper ingested from various sources in poisoning by copper cannot be large, yet they have been shown to be possible factors in producing hemochromatosis. The fact that even small quantities of copper, when ingested over a prolonged period of time, can be damaging should serve as a warning against injudicious dosages and the indiscriminate use of copper compounds in the treatment of anemia.

SANFORD, Chicago.

HEMOPHILIC ARTHRITIS. CHESTER S. KEEFER and WALTER K. MYERS, New England J. Med. **208**:1183 (June 8) 1933.

Five cases of hemophilia are reported in which the lesions of the joints were the outstanding feature of the disease. The changes encountered showed that any or all of the joints may be involved, but the larger joints of the extremities are more commonly the site of hemorrhage. The anatomic changes in the joints correspond closely to those observed in the roentgenogram. The thickening of the synovia and capsule, with the increase in the density of the periarticular tissue, is due to increased fibrosis and the deposition of iron pigment. Subperiosteal hemorrhage frequently leads to erosion of the bone. Subchondral hemorrhage and hemorrhage into the cancellous bone lead to intra-articular and intracancellous cavities. The acute hemarthrosis may be confused with acute pyogenic arthritis. The chronic lesions produced may resemble gout, degenerative arthritis or tuberculosis. There are no absolutely characteristic roentgen changes in the joints. A history of the presence of recurrent and prolonged bleeding in a male patient, with a prolonged coagulation time of the blood, a normal bleeding time and a normal number of blood platelets, establishes the diagnosis.

GENGENBACH, Denver.

RECURRENT OR INTERMITTENT JAUNDICE IN YOUTH. WILLIS E. HARTSHORN, New England J. Med. **208**:1294 (June 22) 1933.

Excluding jaundice in the new-born, of 16 cases of jaundice in patients below the age of 20 years who were recently admitted to the hospital, 6 were diagnosed

as catarrhal; 5 were hemolytic, of which 2 required splenectomy; 3 were of the infectious type; 1 was due to hepatitis, and 1 was diagnosed as due to cholangeitis. The blood picture must be thoroughly investigated before surgical intervention is instituted in persistent jaundice in patients under 20 years of age. The use of 10 per cent calcium chloride as a preoperative measure will eliminate practically all danger from hemorrhage. Splenectomy is indicated in hemolytic jaundice with a large splenic tumor. Diagnosis is often difficult, but necrosis of the liver and death are certain if jaundice persists over a period of years without relief. Exploratory operation is therefore indicated in atypical cases.

GENGENBACH, Denver.

WILL CRETINISM BECOME ENDEMIC IN WISCONSIN? CHARLES H. STODDARD, Wisconsin M. J. **32**:389 (June) 1933.

Cretinism in the United States is reviewed.

Wisconsin is in the goiter region and contains a large number of goitrous persons. "Goitre is the first step on the road to cretinism" (Morel). The lack of great prevalence of cretinism in this state in the past is due to the relatively short time that a large number of people have lived here, many of them having immigrated from nongoitrous regions. In succeeding generations there is an increasing proportion of cretins, which bears out the iodine-thyroid-cretinism relation. The proportionate number will continue to increase, and unless vigorous prophylaxis against goiter is observed cretinism will become a problem of considerable importance.

Sixty-eight cretins, mostly from institutions in southern Wisconsin, are listed.

JANNEY, Milwaukee.

COUGH IN CHILDHOOD. ALAN MONCHIEFF, Brit. M. J. **1**:305 (Feb. 25) 1933.

The author describes by careful analysis various causes of cough, to enumerate, coughs caused by inflammation of the nose and of the nasopharynx, coughs specifically of pharyngeal origin, those due to conditions within the larynx alone and those due to conditions within the trachea alone. Bronchitis and all inflammations of the lungs are described. Special stress is laid on pleurisy, serous or purulent, as a cause of cough. So-called stomach cough is given little attention. Finally, the habit cough is discussed. Under conditions of the trachea, special attention is paid to enlarged glands with various kinds of pressure.

ROYSTER, University, Va.

HEPATOMEGALY WITH PERSISTENT KETONURIA IN A CHILD. C. WORSTER-DROUGHT, Brit. M. J. **1**:403 (March 11) 1933.

The interesting case that is reported is that of a girl, aged 10 years, who had enlargement of the liver and persistent acetone and diacetic acid in the urine, with a total absence of sugar. Her breath had a strong acetone odor. Other children in the family, some of whom had died, were said to have had enlarged livers. The author thinks that there was possibly some familial dyscrasia. He refers to an article by Smith and O'Flynn (*Lancet* **1**:297 [Feb. 11] 1933) which contains the report of a case of similar character. The disease is probably similar to that in a case reported by von Gierke.

ROYSTER, University, Va.

DRY BRONCHIECTASIS. CECIL WALL and J. CLIFFORD HOYLE, Brit. M. J. **1**:597 (April 8) 1933.

The authors discuss dry bronchiectasis, which, according to them, is a condition with a definite clinical picture and certain physical signs and which is characterized by no secretion, although there is occasional hemoptysis. Twenty cases are reported in patients ranging from 5 to 64 years of age, nine of whom were under and

eleven over 15 years. All these cases were studied with the roentgen rays before and after the injection of iodized poppy-seed oil 40 per cent. The outstanding symptom was otherwise unexplained hemoptysis. Cough was a common symptom. There was no cumulative fetid expectoration. Dyspnea occurred in some cases. The constitutional symptoms were mild. The physical signs consisted of occasional clubbing of the fingers and dulness on percussion over the chest, with weak breath sounds. There was crepitation in a few cases, and bronchial breathing was present in four cases. All the patients had previous respiratory infections. The etiology is discussed on a more or less theoretical basis, and no conclusions are reached, though some opinions are expressed.

ROYSTER, University, Va.

NEW GROWTHS OF THE KIDNEY. R. H. JOCELYN SWAN, Brit. M. J. **1**:606 (April 8) 1933.

This article is an analysis of sixty-five cases in which a classification of new growths of the kidney is outlined and the differential diagnosis is discussed.

ROYSTER, University, Va.

AN UNUSUAL CASE OF LYMPHATIC LEUKEMIA. W. E. COOKE, Brit. M. J. **1**:698 (April 22) 1933.

A case of lymphatic leukemia with an apparently fulminant onset and termination is reported. Autopsy showed that the case was probably one of low grade chronic leukemia with a rapid and fatal ending.

ROYSTER, University, Va.

TRANSITORY ARTHRITIS OF THE HIP-JOINT IN CHILDHOOD. RICHARD W. BUTLER, Brit. M. J. **1**:951 (June 3) 1933.

Ninety-seven children suffering from transitory arthritis of the hip joint were studied. The author's summary follows:

Fifty-six of the ninety-seven patients proved to be tuberculous. Thirty-four were suffering from transitory arthritis only, and no abnormality was shown by roentgen examination at any time. Seven had transitory arthritis as a reaction to a localized infection of the bone near the joint, without true infection of the joint. Transitory arthritis without changes indicated by roentgen examination is common in childhood and is frequently diagnosed wrongly as tuberculous. Sometimes it may be of traumatic origin, but more often it is infective, the infection often being secondary to a focus elsewhere in the body. The prognosis of this transitory arthritis is excellent. The results of a follow-up study of twenty-two cases for an average period of three years are given. Transitory arthritis is the most difficult problem in differential diagnosis of tuberculous arthritis of the hip in childhood. Its differentiation from tuberculous and other types of arthritis is discussed.

ROYSTER, University, Va.

ENLARGEMENT OF LYMPHATIC GLANDS IN CHILDREN. P. L. HIPSLEY, M. J. Australia **1**:368 (March 25) 1933.

The author briefly reviews the physiology of the lymph glands and then discusses the various conditions which are responsible for their enlargement.

TENNEY, Madison, Wis.

PROGRESSIVE OSSIFYING MYOSITIS: A CLINICAL AND ROENTGEN STUDY. H. L. ROCHER, Arch. d'électric. méd. **40**:13 (Jan.) 1932.

This is a complete record of a remarkable condition observed in a child, aged 4½ years; it originated at 11 months of age. Some of the osteomas caused a raised appearance of the skin. There were discrete ossifications anterior and posterior to the cervical vertebrae; large cysts of the bone of the vertebral canals were attached

to the vertebrae in the dorsal region; extensive osteomas were present on the right side in the dorsalis and the pectoralis major muscles and on the left side in the dorsalis and in the infraspinous fossa; a large osteoma extended the length of each humerus; there were small osteomas of the abdominal muscles and elsewhere. Histochemical examination showed that these were ossified hematomas resulting from rupture of the arterioles in the muscles.

VINTON, Brooklyn.

SANTONIN IN THE TREATMENT OF INFANTILE ASCARIASIS. N. P. SCHIKHOBALOVA and M. S. BRANBOURG, Arch. de méd. d. enf. **36**:352 (June) 1933.

The failure of santonin in certain cases of infestation with round worms because of the degree of invasion, the method of administration, the condition and technic of administration or improper dosage is a matter of common knowledge. With the object of determining the proper dosage, Schikhobalova and Branbourg conducted an extensive survey in the various children's clinics of Moscow. In this study more than 1,200 patients were treated with santonin. Numerous cases are cited in detail. The conclusions reached are:

1. An exact dosage corresponding to the age of the patient is essential to success.

2. In practice, a daily dose (for two days) of 0.015 Gm. for each year of age is recommended.

3. This dosage is offered either in three portions, with an interval of one hour, or in two portions, with an interval of two or three hours.

AMESSE, Denver.

INFECTION AND REINFECTION IN INFANTS. L. RIBADEAU-DUMAS and RAULT, Nourrisson **21**:79 (March) 1933.

In most infants a first infection, especially of the upper respiratory type, is benign. Reinfections may become progressively more severe and may be accompanied by loss in weight and by diarrhea. In this type of infection the infant seems to lose its resistance, has repeated respiratory infections and often dies at about the end of the first year. In other infants benign infections may be succeeded by severe infections, but the infants are able to develop sufficient immunity to overcome the more severe infection. Subsequent infections become milder, and these infants survive. Athreptic infants may succumb to respiratory infections in the first few weeks of life without showing the usual signs of infection. The course may be afebrile, or the temperature may run a subnormal course.

McCLELLAND, Cleveland.

THE INTRADERMAL SALINE TEST. M. LELONG and Y. PETROVITCH, Nourrisson **21**:141 (May) 1933.

The intradermal saline test is the test described by McClure and Aldrich in 1923. It consists in injecting 0.2 cc. of physiologic solution of sodium chloride intradermally and noting the time required for absorption.

The time of absorption varies with the age, from eleven minutes during the first week to thirty-seven minutes at the age of 3 years. There is a striking parallelism between the curve for absorption and that for weight. This is especially noticeable during the postpartum decline. An increase in the time required for absorption anticipates an increase in weight by a day or two. In states of acute dehydration, e. g., cholera infantum, as one would expect, the tissue thirst is reflected in a more rapid absorption of the saline solution. Artificial febrile states are accompanied by a lowered time of absorption. Contrariwise, in athrepsia and in moribund conditions there is a marked delay in the disappearance of the saline wheal. Insulin accelerates absorption, while the action of thyroid extract is not consistent. A paradoxic reaction is observed in cases of edema, in which the rapid absorption of the injected saline solution comes as a surprise. Satisfactory explanations for the unusual reactions are not offered.

McCLELLAND, Cleveland.

RHEUMATIC MYOCARDITIS WITH NODULES. J. C. NAVARRO, A. F. AJA and A. MARANO, Arch. med. d. hosp. Ramos Mejia **15:** 90 (Sept.) 1932.

A boy, aged 10 years, died after a two months' illness with typical myocarditis. Observations at autopsy showed pulmonary edema and pericarditis. The pericardial sac contained 60 cc. of fluid. The myocardium showed fibrosis and many Aschoff nodules.

SANFORD, Chicago.

HEPATIC ABSCESS DUE TO TRICHOMONAS HOMINIS. J. C. NAVARRO, S. DE ALZAGA and H. M. BERISSO, Arch. med. d. hosp. Ramos Mejia **15:**124 (Sept.) 1932.

A boy, aged 7 years, had been ill for eleven days, with a temperature of 39 C. (102.2 F.). This was accompanied by abdominal discomfort and by the expectoration of foul chocolate-colored material. The blood showed 17,000 white cells, 77 per cent of which were neutrophils. Death occurred within a little over a month; permission for autopsy was not obtained. The organisms can be found only in fresh material and are best viewed by reflected light. They are frequently overlooked. An excellent bibliography of references to this condition is given.

SANFORD, Chicago.

THYMIC HYPERTROPHY. J. ALFREDO FIGUERAS, Arch. de med. inf. **2:**90 (March) 1933.

The diagnosis of enlarged thymus is difficult. The roentgenogram offers the only method of affirming or denying it. Thymic death may be due to some mechanical cause, as well as to a toxic one due to thymic dysfunction, in the same manner that diphtheria toxin sometimes produces sudden death. The most effective treatment and that which brings about most rapid results is radiotherapy.

SANFORD, Chicago.

RHEUMATISM IN INFANCY. MARTINEZ VARGUS, Med. de los niños **33:**249 (Sept.) 1932.

This is an exhaustive review of the subject, running through six succeeding numbers of the *Medicina de los niños*. Under "rheumatism" are included all chronic articular diseases, more or less advanced arthropathies whether or not accompanied by particular pathologic changes and muscular and neuralgic symptoms of toxic or infectious origin.

The various theories of the origin of rheumatic fever are discussed with particular emphasis on the experimental work on rats by Lantier and Alexandresco, who were able to demonstrate a diplostreptobacillus as a possible etiologic agent. In a large series of collected cases the disease is shown to have a distinct age incidence, 70 per cent occurring between the tenth and fifteenth years. The disease has been reported in the first month of life. It occurs in both sexes with the same frequency, being most common in the spring, and many authors believe that heredity and constitutional development play an important part. That it is contagious is evidenced by the epidemics that have been reported.

Two kinds of pathologic lesions are found in rheumatism: first, the congestive type, which is followed by an infiltration of lymphatic exudate between the cells and edema, and second, the specific type, or the nodules of Aschoff.

DWYER, Kansas City, Mo.

SEROFIBROUS INTERLOBAR PLEURISY WITH SPONTANEOUS PNEUMOTHORAX. C. PERNETTA, Rev. brasil. de pediat. **1:** 35 (April) 1933.

A case of serofibrous interlobar pleurisy with spontaneous pneumothorax is reported in a girl, aged 5 years. Roentgenograms are shown. Recovery took place within about three months. The cause may be primary, as tuberculosis or rheu-

matic fever, or secondary, following pulmonary tuberculosis, bronchopneumonia, influenza, scarlet fever, typhoid fever and other acute infections. The prognosis is good if the general condition of the child is good. The author recommends rest in bed, attention to diet and to hygiene, the administration of calcium chloride to hasten calcification and subcutaneous injections of autoserum obtained by exploratory puncture.

SANFORD, Chicago.

ENLARGEMENT OF THE HEART IN EARLY CHILDHOOD. E. PÜSSCHEL, Arch. f. Kinderh. **99**:193 (June 23) 1933.

A case of idiopathic hypertrophy of the heart in a male infant, aged 1 year, is reported. Rickets was the only abnormal finding, excepting the large heart. The cardiac outline was smaller after five weeks of observation and had diminished to normal size after one year. The sixteen cases of idiopathic dilatation of the heart reported since 1927 are reviewed and discussed by the author, supplementing the work of Stoloff, who reviewed all the cases reported previous to 1927.

LEMASTER, Evanston, Ill.

ESOPHAGOSPASM, ESOPHAGOTRACHEAL FISTULA AND CHRONIC ASPIRATION PNEUMONIA. J. DUKEN, Arch. f. Kinderh. **99**:208 (June 23) 1933.

A girl, aged 6½ years, had been treated for bronchiectasis by several physicians. After admission to the hospital, fluoroscopic examination showed spasm of the lower end of the esophagus, with enormous dilatation above it, in addition to signs of bronchiectasis and bronchopneumonia. The general health and nutrition were greatly improved by gavage feedings, but after a few months the child died of pneumonia. At autopsy, a fistula between the trachea and the upper end of the esophagus was found, besides the pathologic condition already known to be present. The author discusses the difficulties in diagnosis encountered in this case.

LEMASTER, Evanston, Ill.

HEPATIC ABNORMALITY AS A CAUSE OF DISTURBED GROWTH. EGON UNSHELN, Monatschr. f. Kinderh. **57**:418, 1933.

This article consists of the report of a case and photographs. A marked disturbance of growth was associated with a marked enlargement of the liver, which was perhaps due to cirrhosis.

GERSTLEY, Chicago.

CONSERVATIVE TREATMENT OF PYLOROSPASM. C. WIENER, Monatschr. f. Kinderh. **57**:441, 1933.

The author is satisfied that atropine is an efficient drug in the treatment of pylorospasm in infants. However, in some cases the patient reacts to the toxicity of atropine before the required amount can be given. Wiener recommends a proprietary remedy derived from atropine. He says that his results were excellent.

GERSTLEY, Chicago.

ROENTGEN TREATMENT OF NONSPECIFIC INFLAMMATIONS. LEONORE LIEBENAM and HERBERT SCHONFELD, Monatschr. f. Kinderh. **58**:104, 1933.

On the basis of 573 observations, the authors conclude that roentgen treatment is of unquestioned value in acute and subacute lymphadenitis as well as in certain phlegmons of the head, such as Ludwig's angina. In other processes and infections, as, for instance, erysipelas, the results are highly questionable. In acute osteomyelitis no favorable results were obtained except, for some unknown reason, in calcaneus in infants. In chronic osteomyelitis the results are more favorable.

GERSTLEY, Chicago.

THE ROENTGENOLOGIC PICTURE OF ADDISON'S DISEASE. CARL HUNERMANN, Monatschr. f. Kinderh. **58**:124, 1933.

The author reports a case of Addison's disease with two x-ray pictures demonstrating calcified areas in the suprarenals.

GERSTLEY, Chicago.

METABOLISM AND THE DIFFERENTIAL DIAGNOSIS OF GLYCOGEN DISEASE. H. BEUMER and A. LÖSCHKE, München. med. Wchnschr. **80**:377 (March 10) 1933.

The clinical symptoms of glycogen disease may be observed during the first year of life. The upper part of the abdomen becomes prominent, owing to enlargement of the liver; there are chronic hypoglycemia, acetone in the breath and urine and a constant desire to eat carbohydrates. The hypoglycemia due to deficient glycogenolysis differs from that due to hyperinsulinemia in that it is not affected by the injection of suprarenin but only by the ingestion of carbohydrate.

The abnormal carbohydrate metabolism also affects the metabolism of other substances, such as fat. In a 4 year old child with glycogen disease the authors found constant lipemia. The total amount of fat as well as of cholesterol in the serum was from two to three times the normal content. After the ingestion of 150 cc. of cream (28.4 per cent fat), the serum values given in the accompanying table were obtained in the patient and in a child of the same age used as a control.

Serum Values

	Patient		Control	
	Total Fat	Cholesterol	Total Fat	Cholesterol
During fasting	1.08	0.390	0.540	0.156
After 4 hours	1.88	0.480	0.880	0.142
After 8 hours	2.84	0.540	0.480	0.126
After 24 hours	1.68	0.498	0.440	0.124

Normally the lipemia reaches its height after four hours and returns to normal after eight hours. In the patient with glycogen disease the amount of fat and cholesterol were above the values obtained during fasting after twenty-four hours.

The lipemia in glycogen disease and that in diabetes are similar, in that both are due to a deficiency in carbohydrate metabolism and associated with a tendency to acidosis. However, in glycogen disease there is hypoglycemia, and in diabetes, hyperglycemia. In glycogen disease, insulin is contraindicated and a diet high in carbohydrate and low in fat is necessary. There are cases of cirrhosis of the liver in childhood in which the condition may simulate glycogen disease in that there are hepatomegaly, hypoglycemia and a tendency to acetonuria. However, in cirrhosis there is frequently an enlarged spleen, and there is no abnormality in the fat metabolism after the ingestion of a meal high in fat, as is observed in glycogen disease.

BRAHDY, Mount Vernon, N. Y.

THE HISTOLOGIC PICTURE OF RHEUMATIC FEVER: IX. THE SCIATIC NERVE IN RHEUMATISM. J. KOEPPEN, Virchows Arch. f. path. Anat. **283**:303, 1932.

The author made careful histologic studies of the sciatic nerve in thirty-seven patients from 22 to 86 years of age. Three of the eight patients with acute or subacute rheumatic disease whose organs were studied by Klinge showed swelling of the walls of the smallest vessels within the nerve, with and without round cell infiltration, and numerous perivascular infiltrations with lymphocytes. In nine patients with old rheumatic disease, no morphologic changes in the nerve were found. In three patients with a history of unilateral chronic "sciatica" and anatomic signs of recurrent endocarditis, the arteries supplying the sciatic nerve of

the involved side showed severe sclerosis of the intima and advanced calcification of the media, whereas those of the healthy side presented only slight arteriosclerosis. In six patients with sepsis, no cellular infiltrations of the sciatic nerve were found. As a control, ten patients were studied who had died from diseases such as tuberculosis, tumors, syphilis and diabetes mellitus. They did not reveal changes similar to those seen in rheumatic disease. The author believes that the histologic changes in the nerves in the patients with acute rheumatic fever are due to the rheumatic virus, and that in the patients with clinical sciatica and recurrent endocarditis, the arteriosclerosis may have developed on the basis of old rheumatic arteritis.

SCHOENTHAL, New York.

THE HISTOLOGIC PICTURE OF RHEUMATIC FEVER: VII. THE FREQUENCY OF COINCIDENCE OF ARTHRITIS DEFORMANS AND CHRONIC ENDOCARDITIS. (THE RELATION BETWEEN CHRONIC INFLAMMATION AND DEFORMING ARTHRITIS.) NOTKER GRZIMEK, Virchows Arch. f. path. Anat. **286**:286, 1932.

In 520 unselected cases in which the knee joints could be examined at autopsy, marginal granulations (exostoses), which are pathognomonic of arthritis deformans, were found in 91 cases. Thirty-nine (42.8 per cent) of these 91 cases of genuine arthritis deformans showed definite evidence of an old or recurrent endocarditis. Among the remaining 429 cases, similar lesions of the endocardium were found in only 77 (17.9 per cent). Fifteen cases of arthritis deformans without endocarditis (16.5 per cent) showed evidence of chronic inflammation of the gallbladder.

SCHOENTHAL, New York.

THE HISTOLOGIC PICTURE OF RHEUMATIC FEVER: VIII. THE REACTIONS OF THE FIBERS OF THE COLLAGEN CONNECTIVE TISSUE IN RHEUMATISM AND IN OTHER INFLAMMATIONS. F. SCHOSNIG, Virchows Arch. f. path. Anat. **286**:291, 1932.

Klinge's investigations have shown that one of the first histologic changes in rheumatic fever is the fibrinoid swelling of the connective tissue. This fibrinoid inflammation affects the matrix of the connective tissue in such a way that the collagen fibers of rheumatic infiltrations will take a silver stain (method of Tibor-Papenheim-Bielschowsky) readily.

In this paper, Schosnig shows that in rheumatic disease, destruction and solution of the fibers of the connective tissue occur only occasionally, whereas in other diseases associated with fibrinoid inflammation of the connective tissue, such as syphilitic gumma, tuberculosis and diphtheria, complete necrosis of the tissue with complete destruction of all constituents is much more frequent. Therefore, the silver staining of the fibers can be of diagnostic help in cases of fibrinoid inflammation.

SCHOENTHAL, New York.

THE HISTOLOGIC PICTURE OF RHEUMATIC FEVER: X. THE UPPER AIR AND FOOD PASSAGES IN RHEUMATISM. D. SARAFOFF, Virchows Arch. f. path. Anat. **286**:314, 1932.

In seven unselected cases of definite rheumatic disease in patients from 5 to 28 years of age which have been reported by Klinge, the tissues of the organs of the neck were studied in serial sections. Rheumatic lesions, such as circumscribed swelling of the matrix of the connective tissue, granulomas containing varying quantities of cells and fresh or old scars were found in six of these cases. These lesions were located below the mucous membranes of the upper air passages, within the exterior and interior muscles of the larynx, between the muscle fibers of the pharynx, in the muscle layers of the esophagus, in the capsule of the thyroid gland, in the peritracheal and periesophageal tissue and in other places. The tonsils and adenoids failed to reveal any changes typical

of rheumatic disease, in contradistinction to the peritonsillar tissue, which was markedly involved in four of the seven cases. In the remaining three cases, no lesion could be found in the peritonsillar tissue. No conclusions could be drawn as to a special portal of entry of the rheumatic virus, since the lesions showed various distribution in the different cases. There is no evidence which would indicate that the tonsillar tissue is the sole portal of entry, since signs of nonspecific inflammation were found in the mucous membranes of the pharynx and larynx.

SCHOENTHAL, New York.

THE HISTOLOGIC PICTURE OF RHEUMATIC FEVER: XI. FINDINGS IN TONSILS REMOVED BY OPERATION. F. KLINGE, Virchows Arch. f. path. Anat. **286:** 333, 1932.

Serial examinations were made of the tonsils of two patients, one a man, aged 20, and the other a boy, aged 11 years, who had suffered from attacks of acute rheumatic fever for three weeks and five months, respectively, prior to the removal of the tonsils. They revealed rheumatic infiltrations in the paratonsillar tissue in various stages of development, as described in previous papers.

In a third patient (27 years old), whose first attack of rheumatic fever occurred two months prior to tonsillectomy, a few small foci were found in the peritonsillar tissue.

In five other patients who gave a similar history, no specific rheumatic changes in the peritonsillar tissue could be detected.

SCHOENTHAL, New York.

THE HISTOLOGIC PICTURE OF RHEUMATIC FEVER: XII. CRITICAL EVALUATION OF THE HISTOLOGIC SPECIFICITY OF THE RHEUMATIC CHANGES IN THE TISSUES. F. KLINGE, Virchows Arch. f. path. Anat. **286**:344, 1932.

In this communication Klinge summarizes the changes which he and his co-workers found in the organs of persons suffering from acute rheumatic fever and its chronic forms, such as chronic (recurrent) articular rheumatism and chronic (recurrent) visceral rheumatism. The manifestations of rheumatic disease may be present in various combinations, but the uncomplicated forms of the disease allow a differentiation between the specific rheumatic changes and those seen in other diseases. The histologic changes in the organs have been described in previous papers. The rheumatic virus chiefly affects the connective tissue and causes: (1) edema and fibrinous swelling of the matrix with relative conservation of the fibers and (2) enlargement and granulation of the connective tissue cells. In addition, marked parenchymatous lesions of the smooth and striped muscles and, to a lesser degree, of the liver, kidneys and brain have been observed. A nonspecific lymphocytic and polymorphonuclear infiltration of the tissues completes the picture. These changes are not different from those seen in other chronic nonpurulent septicemias in which organisms (cocci) are regularly found and identical nodules have been observed in scarlet fever and in experimental serum sickness. In rheumatic disease, however, the fibrinoid swelling *(rheumatisches Fruehinfiltrat)* and the proliferative changes (granuloma or Aschoff's nodule or tendon nodule) are more marked than in any other disease.

It is not possible to give the details of the amazing amount of work which is contained in the twelve well illustrated papers by Klinge and his co-workers, which should be read in the original by all those interested in the problem of rheumatic disease.

SCHOENTHAL, New York.

RETICULOSARCOMATOSIS (RETICULO-ENDOTHELIOSIS OF SARCOMATOUS NATURE). E. BENECKE, Virchows Arch. f. path. Anat. **286**:693, 1932.

A boy, aged 4½ years, suffered from pain in the epigastrium and increasing distention of the abdomen. There were no symptoms except poor appetite and

insomnia. On admission to the hospital, several nodes were felt in the epigastrium. Examination of the blood showed slight anemia. A laparotomy was performed, and a tumor mass was found which involved the head of the pancreas. A small piece of this mass was diagnosed as reticulosis; a diagnosis of tumor, however, could not be excluded. Repeated roentgen treatments were given. About eight weeks after the onset of the disease and a few days before death, the temperature rose to 39 and 40 C. (102.2 to 104 F.), and the child died with the signs of heart failure. At autopsy a large tumor evidently originating from the retroperitoneal lymph nodes was found. The head of the pancreas was involved, and the left suprarenal gland was destroyed. Metastases were found in the liver, the pleura, the cervical and hilar lymph nodes and in the lymph nodes along the aorta and at the roots of the lungs and the liver. There were an enlargement of the spleen and a pseudomembranous inflammation on the left side at the root of the tongue. The latter was diagnosed, histologically, as diphtheria, though no Löffler bacilli could be found. This diagnosis seemed justified, since the heart and spleen showed changes typical of diphtheria. The microscopic examination of the organs revealed the presence of a reticulo-endotheliosis which involved the reticulum cells of the spleen, the lymph nodes, the tonsils and the bone marrow, and the Kupffer cells, and the endothelial cells of some lymph nodes. In some parts of the tumor-like growth streptococci, staphylococci and a few gram-negative bacilli were found, but in contradistinction to Akiba and Guizetti, the author does not consider them as the etiologic agent. The author's case resembles, to a certain degree, that described by Tschistowitsch and Bykowa; the tumor-like growth, however, is similar to that in the cases described by Roessle and Roulet.

In the presence of a generalized involvement of the Kupffer cells of the capillaries and of the reticulocytes of the spleen, liver, lymph nodes and tonsils, the diagnosis of reticulosarcomatosis indicating a systemic disease seems to be justified.

SCHOENTHAL, New York.

FURTHER CONTRIBUTION TO THE KNOWLEDGE OF THE RETOTHEL SARCOMA OF THE LYMPH NODES AND OF OTHER LYMPHOID ORGANS. F. ROULET, Virchows Arch. f. path Anat. **286**:702, 1932.

In a preceding paper (*Virchows Arch f. path. Anat.* **277**:15, 1930) the author discussed his attempts to separate a new type of tumor from the ordinary lymphosarcoma. The tumor consists chiefly of cells derived from the retothel (reticulocytes) which preserve their typical netlike arrangement in the new growth. The structural peculiarity seems to justify the separation of the tumor (retothelsarcoma) from those composed of lymphatic and endothelial cells.

In this paper, the author describes a number of cases, one of which was in a boy, aged 11 years, in whom the tumor originated from the upper epipharynx. This shows that there are similarities between the systemic hyperplastic reticulosis and this type of tumor. It is difficult to draw a sharp line between the different types of proliferation of the reticulo-endothelial system which differ mainly in the type of cell which is preponderant. The clinical picture and the prognosis seem to be similar.

SCHOENTHAL, New York.

CARDIAC BRONCHOSTENOSIS AND ATELECTASIS IN CHILDHOOD. H. LAUENSTEIN, Ztschr. f. Kinderh. **54**:145, 1933.

The author calls attention to stenosis and atelectasis which follow enlargement of the left auricle in mitral disease in children. Owing to its anatomic situation, the left main bronchus is very likely to become stenosed by pressure from adjacent organs, especially by the enlargement of an auricle. The signs of stenosis may be detected best over the fifth interspace posteriorly. The atelectasis which follows may simulate pneumonia.

SHELLING, Baltimore.

CONGENITAL DESTRUCTIVE TUMORS OF THE KIDNEYS IN CHILDREN. M. MIKULA and F. KLEIN, Časop. lék. česk. **70**:1820 (Dec. 18) 1931.

Renal tumors in children are mixed rather than epithelial, as in adults, and make up 20.4 per cent of all tumors in contrast to 0.5 per cent in adults. In the authors' series of 54 malignant tumors in children, 16 were congenital renal tumors. Of the 16, 11 were in children under 5 years of age; 2, in children under 6 and only 3 in children about 10 years of age. Hematuria was present, according to the literature, in from 10 to 16 per cent of the cases, and Steffen found it present in only 18 of a series of 219 cases. This is because, although the tumor is within the kidney, it does not involve renal tissue in either the early or the late stages. Fever is a frequent early symptom, and albuminuria is often present. Differential diagnosis includes perinephritic abscess, hydronephrosis, cystic kidney and tumors of the liver and spleen, the mesenteric gland and the rectum and cecum. The reports of 5 of a series of 16 cases are given with the histologic findings. The benign tumors are adenomas, fibromas and benign hypernephromas, and the malignant tumors are sarcomas, malignant hypernephromas and mixed tumors. In a series of 422 cases of sarcoma of the kidneys, Steffen reported 80, or 18.8 per cent, in children. The most malignant tumors are the polymorphous sarcomas. In a series of 146 cases of malignant tumor cited, carcinoma of the kidney was reported in 11 cases, or 7.5 per cent. Surgical intervention is indicated except in bilateral involvement, metastases or severe cachexia. Of the author's 16 patients, 3 died shortly after operation and 5 were apparently cured after periods of from one and one-half to eight years.

STULIK, Chicago.

LEUKEMIC BILATERAL EXOPHTHALMOS. E. MESROPIAN, Sovet. vestnik oftal. **1**:558, 1932.

In a child, aged 2, suffering from monocytic leukemia, bilateral exophthalmos developed within two days. There was marked chemosis; the cornea and iris were normal. Ophthalmoscopic examination revealed only a pale hue of the fundus. The spleen was greatly enlarged; the temperature was elevated to 103 F. The blood count was as follows: hemoglobin, 44 per cent; erythrocytes, 2,490,000; leukocytes, 93,900; lymphocytes, 18.5 per cent; monocytes, 64.5 per cent. The child was taken from the hospital in a semiconscious condition by the parents.

SITCHEVSKA, New York. [ARCH. OPHTH.]

CHEMICAL CHANGES IN THE BLOOD AND TISSUES IN CONGENITAL HYPERTROPHIC PYLORIC STENOSIS. E. SCHNOHR, Acta pædiat. **14**:49 (Nov. 30) 1932.

The chloride content of the serum, whole blood, urine and stomach was studied in nine cases of pyloric stenosis and in fourteen cases representing loss of chloride through vomiting or diarrhea. Hypochloremia was found to run fairly parallel with the severity of the symptoms, especially when the symptoms were of long duration. When the serum chloride was low, there was likely to be an accompanying elevation of serum nonprotein nitrogen and a depression or even disappearance of urinary chloride. Under these conditions the chloride of the gastric contents was also at a low level. Free gastric hydrochloric acid was seldom present, but the total acidity was not greatly decreased; this was interpreted as evidence of the buffer effect of the proteins of gastric secretions. Two patients who died during hypochloremia showed low chloride levels in the skin, lungs and kidneys, and normal levels in the muscles, spleen and liver. In therapy, intramuscular injections of a 3 per cent solution of sodium chloride failed to restore the blood chloride level to normal and were abandoned in favor of hypodermoclyses of a 0.9 per cent solution of sodium chloride.

MCINTOSH, New York.

A Contribution to the Knowledge of Primary Anemic States in Early Infancy. Y. Åkerrén, Acta pædiat. **14**:142 (Nov. 30) 1932.

Two cases of early anemia are described. In one, the hemoglobin was 30 per cent (Sahli) and the red cell count 1,100,000 at 5 weeks of age; in the other, the hemoglobin was 35 per cent and the red cell count, 1,900,000 at 1 week of age. One of the patients contracted a somewhat severe degree of physiologic jaundice. In both of the patients the existence of a causal infection was postulated but not proved. Both patients recovered under ordinary therapeutic measures.

McIntosh, New York.

A Contribution to the Study of the Incubation Period of Acute Epidemic Hepatitis. M. Lindquist, Acta pædiat. **14**:166 (Nov. 30) 1932.

Those who interpret "acute catarrhal jaundice" as an infectious disease agree that it must have an incubation period, but hold divergent views regarding its length. The possible limits have been given as anywhere from three days to as many months, though recently there has been a tendency to regard the incubation period as varying ordinarily between two and four weeks.

Five case histories are presented. The lower limit of the incubation period in this small series is between nineteen and twenty-seven days; the upper limit is between twenty-six and thirty-five days.

McIntosh, New York.

Polycythaemia Vera in Childhood. T. Halbertsma, Maandschr. v. kindergeneesk. **2**:1 (Oct.) 1932.

A case of polycythemia in a boy of 6 years is described. The child had a red complexion, enlargement of the spleen, a tower skull, hypospadias and a crooked little finger; he was very active, had no dyspnea and suffered from attacks of headache. Vitium cordis could be excluded. During a control period of one year the condition of the child remained stationary. The sedimentation rate of the blood corpuscles was low and the total blood volume highly increased. As a case of tower skull, the condition should be classified with the group of acrocraniodyshemia of Günther; as a case of polycythemia, it belongs to group I of Hottinger, for it is an isolated case, dissimilar to various dystrophic conditions.

van Creveld, Amsterdam, The Netherlands.

Nervous Diseases

Rôle of the Anterior Roots in Visceral Sensibility. Theodore T. Stone, Arch. Neurol. & Psychiat. **30**:99 (July) 1933.

The author demonstrated that sensations of visceral pain are not carried over the anterior root as has been described. If a sufficiently large number of posterior roots are sectioned, visceral pain is abolished.

Beverly, Chicago.

The Argyll Robertson Pupil: An Anatomic-Physiologic Explanation of the Phenomenon, with a Survey of Its Occurrence in Neurosyphilis. H. Houston Merritt and Merrill Moore, Arch. Neurol. & Psychiat. **30**: 357 (Aug.) 1933.

The Argyll Robertson pupil is caused by a destruction of the pupillary light reflex fibers and the sympathetic fibers. These fibers run together for a short distance in the anterior end of the brain stem just ventral to the posterior commissure. Any lesion at this point would produce the phenomenon, but the only condition causing it in cases so far reported, with the exception of a few cases of gliomatous invasion of this region, has been syphilis.

Beverly, Chicago.

FAMILIAL SPASTIC PARALYSIS: REPORT OF THREE CASES IN ONE FAMILY AND OBSERVATION AT NECROPSY. HARRY A. PASKIND and THEODORE T. STONE, Arch. Neurol. & Psychiat. **30**:481 (Sept.) 1933.

The authors reported three cases of familial spastic paralysis in one family. This is a rare familial disease (there are 150 families reported in the literature). The outstanding symptom is spasticity. The symptoms may not appear until the age of 10 years or may date from birth. Defective mental development, convulsions, optic atrophy, nystagmus, extra-ocular palsies, disturbances in speech and muscular atrophies may occur. Pathologically, there are microcephaly, agyria and absence of some of the association fibers.

BEVERLY, Chicago.

SPHENO-OCCIPITAL CHORDOMA: REPORT OF A CASE. MEYER CANTOR and LOUIS D. STERN, Arch. Neurol. & Psychiat. **30**:612 (Sept.) 1933.

Chordomas are malignant processes arising from the remnants of the notochord. They may occur at any point along the vertebral column but are most frequent at the upper and lower extremities. A case of spheno-occipital chordoma with autopsy is reported. Chordomas are characterized by their readiness to invade bone. They seldom metastasize and rarely invade the brain itself.

BEVERLY, Chicago.

DWARFISM AND OCULAR DEFECTS IN HEREDOFAMILIAL DISEASE OF THE CENTRAL NERVOUS SYSTEM. BELA MITTELMANN, Arch. Neurol. & Psychiat. **30**:621 (Sept.) 1933.

Four relatives presenting an unclassified type of hereditary familial disease of the nervous system are described. There were stunting of growth, signs of involvement of the pyramidal tract, cerebellar disturbance, nystagmus, mental retardation and changes of the cranial nerves. The symptoms were described as a result of an exaggeration of the recessive abiotrophic tendencies present in the generation to which the patients belonged.

BEVERLY, Chicago.

TRAINING OF THE NEUROLOGIST, THE NEUROPSYCHIATRIST AND THE PEDIATRICIAN. ROBERT S. VEEDER, Arch. Neurol. & Psychiat. **30**:628 (Sept.) 1933.

This is an excellent article dealing with the relationship of the neuropsychologist and the pediatrician. The pediatrician's practice is general and limited to an age group; he is primarily concerned with preventive medicine and is dealing with a constantly changing and maturing organism. He sees the child as a whole. When problems which require a special technic for treatment arise he calls in consulting specialists, for example, the urologist. Mental problems which are the result of wrong training, for example, enuresis, can be handled by the pediatrician. If there is evidence of potential danger to the patient when he becomes an adult, a psychiatrist who understands the mental disorders of adults should be consulted. Clinics for mental hygiene and clinics in children's hospitals should be a part of the medical school rather than a distant, isolated unit.

BEVERLY, Chicago.

ENCEPHALOGRAPHY IN INFANTS AND CHILDREN. MORRIS GLEICH, Arch. pediat. **50**:449 (July) 1933.

The author discusses the various indications for encephalography. He believes that this procedure is a help in diagnosis in some instances in which thorough physical and neurologic examinations are not sufficient to enable one to make an accurate diagnosis. He thinks that it is particularly useful in trauma to the brain or skull, tumors of the brain, epilepsy and degenerated lesions of the brain.

WADDELL, JR., University, Va.

EPILEPSY IN CHILDREN. HOWARD R. COODER, California & West. Med. **39**:169 (Sept.) 1933.

A study of 100 cases of epilepsy in children is presented. The cases are classified according to the clinical varieties of epileptic seizures, which are described. Treatment of epilepsy is discussed, with the results obtained by the use of various methods of therapy.

MARSHALL, San Francisco.

STERILIZATION OF THE FEEBLE MINDED. H. A. BRUCE, Canad. M. A. J. **29**:260 (Sept.) 1933.

The author discusses race degeneration as one of the menaces of the age. The conclusion reached is that it is common sense to insist, as twenty-seven of the forty-eight states of the United States of America have insisted between 1907 and 1931, that persons with mental deficiency be compulsorily sterilized.

MOORE, Omaha.

FRIENDSHIPS AND QUARRELS AMONG PRESCHOOL CHILDREN. ELISE H. GREEN, Child Development **4**:237 (Sept.) 1933.

By means of a thirty second observation technic, the author conducted a study of forty nursery school children, in order to ascertain the relative rôles of group play and quarreling in the socialization of the preschool child. Analysis was also made of age and sex differences in social contacts and quarrels, as well as of the types of social play in which quarrels arise. The author concludes that indexes of friendship increase regularly with advancing age. From 2 to 3 years this is due to an increase in the number of friends, whereas from 3 to 5 years there ensues an increase in depth of friendship. Sex differences in friendship were small, the girls having slightly more friends than the boys who, however, formed deeper friendships. Unisexual friendships predominated. The ratio of quarreling to friendships increased with age, boys being slightly more quarrelsome. In fact, quarrelsomeness seemed to depend on the extent to which boys made up the group, boy-boy groups being the most quarrelsome, boy-girl groups less so and girl-girl groups the least. Indexes of friendship and indexes of quarrelsomeness correlated 0.30. Mutual friends were more quarrelsome and mutual quarrelers were more friendly than the average. The author believes, therefore, that quarreling is a part of friendly social intercourse during the nursery school ages.

ABRAMSON, New York.

INFECTION BY INTESTINAL PROTOZOA IN RELATION TO THE INTELLIGENCE OF SIBLINGS. MARGARET SCHELL, Child Development **4**:253 (Sept.) 1933.

A preliminary investigation was made to determine the possible effects of infection of the intestines by protozoa on mental development. The Stanford revision of the Binet-Simon tests of intelligence was given to 156 children from families in which at least one child was infected either with Endamoeba histolytica, Councilmania lafleuri or Giardia enterica, and in which at least one child was normal with regard to these infections. Intelligence quotients were corrected to the mean chronological age of the group, and each infected child was compared with his uninfected siblings. The mean intelligence quotient of the infected group was 97.5 as compared with 97.2 for the control group. The standard deviation for both groups was 14.5, indicating no difference in the variability of the groups. In 52 per cent of 89 pairs, the control siblings had higher intelligence quotients than the infected children, whereas in 48 per cent the infected siblings ranked higher. No significant difference was found, therefore, between the intelligence quotients of the infected group and those of the control group. Nor were differences observed with respect to cooperation, speed, effort and inhibition in the test situations, as well as with respect to personality traits.

ABRAMSON, New York.

THE HERPES ENCEPHALITIS PROBLEM, II. FREDERICK P. GAY and MARGARET HOLDEN, J. Infect. Dis. **53**:287 (Nov.-Dec.) 1933.

This is an excellent review of present conceptions of the problem of encephalitis.

TOOMEY, Cleveland.

PSYCHOANALYTIC PROCEDURE IN THE TREATMENT OF THE NEUROSES OF CHILDHOOD. HERBERT J. CRONIN, M. J. & Rec. **138**:58 (July 19) 1933.

The author gives the case reports of two children suffering from neuroses. The first is that of a girl, aged 12. She ran away from her home one night, leaving a note for her parents saying that she had gone away to meet a tall, masked man who had ordered her to come to him. She was found and returned to her parents. She had complete amnesia for the writing and for her flight from home. The next day she was taken to a physician for examination and treatment. He found her in good physical condition, but her family history revealed that she had been very unhappy at home. She was living with her father and stepmother, who were constantly quarreling. The girl was jealous of her stepmother and loved her father affectionately. It was the Oedipus complex that forced her to run away to meet the tall, masked man. When she described this man, it was found that he resembled her father. There was constant discord between the girl and her stepmother because the latter often criticized the girl's maternal aunts, who had been mother substitutes for her. The girl felt inadequate and inferior. Subtle conflicts stirred up by psychosexual changes of puberty activated new sources of conflict and intensified older conflicts connected with her Oedipus. She was removed to a boarding school and given psychotherapy and active exercise. She was much improved.

Case 2 is that of a boy, aged 12, who lived in the home with his father, toward whom he had an ambivalent regard. He had feelings of trust and distrust, love and hate, confidence and fear. The father forced his will on the boy at all times, and roughly scolded him. His mother had committed suicide, and the boy had witnessed the act. He became nervous and irritable; he slept poorly and ate little. His older brother thought that the boy would either run away from home or have a nervous breakdown. The patient was taken away from home, put in a boarding school and given exercise and psychotherapy. He improved greatly.

Here were two children suffering because of quarrels and conflicts in the home, which they were not able to escape; the one was able to flee from her unhappiness by dissociation, relinquishing conscious control and accepting unconscious control, whereas the other vacillated between neurotic illness and dissociation.

WILLIAMSON, New Orleans.

THE SUBNORMAL CHILD—SEVENTEEN YEARS AFTER. RUTH E. FAIRBANK, Ment. Hyg. **17**:177 (April) 1933.

A group of 122 subnormal children, studied in 1914, was reviewed socially and psychologically in 1931. Campbell, reporting the original survey of this group in the first issue of *Mental Hygiene* (January 1917), divided them into three groups; 12 per cent were seriously handicapped mentally, many being unable to read or write. It was anticipated that this group would add to the ranks of the vagrant, the immoral and the delinquent. The second classification, numbering 53 per cent of the children under survey, was definitely subnormal, although less defective than those of the first class. These, it was predicted, would be found drifting along the lowest social levels. The remaining 45 per cent were borderline or high grade defectives, whose somewhat higher intellectual level was presumably a liability to society by virtue of its delinquency and breeding possibilities. Of these subnormal children, the 122 available for analysis in 1931 consisted of 72 boys and 50 girls. All but 2 of the latter were married. There were 5 cases of illegitimate motherhood among the girls, and 5 of prostitution.

Of the 122 subjects, only 30 had appealed to social welfare agencies in the last seventeen years. Three fourths of the persons were financially independent—this in spite of the economic depression. Most of the boys in the 1917 survey entered the trades and humbler occupations. One of the children in this subnormal group grew up to become a prohibition agent. There was surprisingly little alcoholism among the children of alcoholic parents. Eleven per cent of the entire group had records of more than one court appearance, and 25 per cent had at least one appearance before the juvenile or upper court. The adults with the bad court records, however, were not necessarily the children who had been delinquent as juveniles. Most of the court cases were from the less retarded groups, justifying Dr. Campbell's prediction. Marriage apparently proved to be a stabilizing factor, both economically and emotionally.

Forty of the subjects were retested seventeen years after the original psychometric study. The scores varied little from the original findings; half of the 40 subjects had a mental age of less than 12 at the time of retesting, while the remaining half fell in the dull normal group. Their children, however, placed in somewhat higher psychologic categories.

A corresponding survey was made of a control group of children of normal intelligence, attending the same school. In this group marriage took place at a much later age; delinquency and crime were much less, and the vocational status was much higher. The paper is rich in statistical citation and should be read in full for an adequate understanding of the interpretation of this survey.

DAVIDSON, Newark, N. J. [ARCH. NEUROL. & PSYCHIAT.]

THE CONTRIBUTION OF PHYSICAL ILLNESS TO THE DEVELOPMENT OF BEHAVIOR DISORDERS IN CHILDREN. L. KANNER and S. E. LACHMAN, Ment. Hyg. **17**:605 (Oct.) 1933.

In an article on the influence of disease on the behavior of children, Kanner and Lachman are of the opinion, from an analysis of case records, that the forms which behavior may assume following physical illness may be grouped into three more or less distinct categories: (1) illness followed by no appreciable alteration of existing behavior patterns; a good reaction may sometimes be seen even to very drastic changes resulting from serious illness; (2) illness setting up behavior problems in originally stable children of average or superior intelligence, well developed and well adjusted socially, and members of stable, healthy families, in whom no complaints may be had as to conduct prior to illness, but in whom there is usually a definite relation of the difficulties of behavior to the previous illness; (3) illness setting up, exaggerating or adding to behavior problems in unstable children, emotionally handicapped and brought up in an unstable environment.

The occurrence of behavior difficulties depends on the nature of the illness, the make-up of the child's personality, parental attitudes and reaction tendencies, iatrogenic (physician-determined) tendencies and other incidental factors. The treatment of the behavior difficulties will therefore depend on a careful consideration of the etiologic factor in each case.

ABRAMSON, New York.

A CASE OF CONGENTAL ELEVATION OF THE CERVICAL SPINE ASSOCIATED WITH SYRINGOMYELIA. FELIX DU TOIT, Brain **54**:421 (Dec.) 1931.

The case reported is the second with a special neurologic condition to be described. Marked elevation of the left scapula, shortness of the neck, tilting of the head and scoliosis were the most conspicuous features of the deformity. Sprengel believed that etiologically the deformity was the result of malposition of the fetus in utero, but generally it is attributed to an arrest in development. A Klippel-Feil syndrome (fusion of the cervical vertebrae) was also present. The neurologic disturbances seemed to point to syringomyelia.

MICHAELS, Boston. [ARCH NEUROL. & PSYCHIAT.]

A Case of Haemolytic Streptococcal Meningitis, with Recovery. Hildreth Rockett, Brit. J. Child. Dis. **30**:196 (July-Sept.) 1933.

Meningitis developed in a boy, aged 2½ years of age, following an attack of whooping cough complicated by bronchopneumonia. The first lumbar puncture revealed a turbid fluid under slightly increased pressure, with a cell count of 1,800, mostly polymorphonuclears. No organisms were found on direct smear and the culture was negative. A profuse growth of hemolytic streptococcus in pure culture was obtained from the spinal fluid withdrawn the second day. Treatment by antiscarlatinal serum administered intrathecally and intramuscularly was immediately begun. Further cultures of the spinal fluid were negative. Recovery was considerably retarded by severe paroxysms of whooping cough.

Langmann, New York.

Hydrocephalus Successfully Treated by Repeated Puncture of the Lateral Ventricles. E. C. Warner, Proc. Roy. Soc. Med. **26**:1007 (June) 1933.

The patient, first seen when he was 6 months old, was suffering from headache, screaming and vomiting; there were a large nevus of the face and general enlargement of the head. Punctures of the ventricles were performed, 30 and 20 cc. of clear fluid being removed on each occasion. The screaming continued, and on the third occasion 90 cc. of fluid was removed. The symptoms ceased, and the head actually became smaller. A roentgenogram taken of the head at a recent date showed nothing abnormal.

Williamson, New Orleans.

Cerebellar Tumor, Left Lobe. J. C. Jewesbury, Proc. Roy. Soc. Med. **26**:1018 (June) 1933.

A case of cerebellar tumor was reported in a girl, aged 12. The results of physical and ocular examinations are given in the report. A roentgenogram of the skull (lateral view) showed absorption of the inner table at the summit of the vault, with some local irregularity. The author gives a record of cases of cerebellar tumors in the children's department of St. Thomas' Hospital since 1921.

Williamson, New Orleans.

Infantile Epilepsy and Chronic Mania. R. Benon, Arch. de méd. d. enf. **36**:535 (Sept.) 1933.

In reporting a case of epileptic dementia in a boy of 7 years, Benon discusses the possibility of chronic mania appearing in the course of epilepsy in very young subjects. This complication usually follows a long series of crises and is often mistaken for delirium.

Amesse, Denver.

Treatment of Cerebrospinal Meningitis. G. Paisseau, P. Tournant and G. A. Patey, Arch. de méd. d. enf. **36**:664 (Nov.) 1933.

Repeated failures with antimeningococcus serum, especially since the World War, have provoked numerous substitutions or adjuvants such as bacteriotherapy and proteinotherapy. By way of demonstrating the superlative value of the serum, notwithstanding the prevailing criticism in some quarters, the authors report thirteen cases treated solely by this means, which resulted in cure without sequelae except in two subjects who sustained the loss of vision in one eye through iridochoroiditis. Several of these cases were among nurslings, in whom the mortality is commonly very high. In two other subjects meningitis was complicated with purpura and arthritis. In the treatment of these patients both the intraspinal and intramuscular routes were used. In nine cases the cisternal method was employed, and this avenue is particularly recommended when type B of the meningococcus is involved.

Amesse, Denver

A NEW FORM OF DEGENERATION. CORNELIA DE LANGE, Arch. de méd. d. enf. **36**:713 (Dec.) 1933.

Under the title "Amsterdam Type" de Lange comments on two instances of an unusual form of degeneration found in the children's clinic of the university. Differing markedly from mongolism, the characteristic features of this congenital disorder appear to be physical and mental inferiority, brachycephaly, heavy and connected eyebrows, abnormally small hands and feet, low position of the ears, advanced position of the thumb and thenar eminence and syndactylism.

The report is adequately illustrated.

AMESSE, Denver.

A CASE OF MENINGO-ENCEPHALITIS IN AN INFANT AGED 9 MONTHS. S. GRACOSKI, Bull. Soc. de pediat. de Iasi **3**:118 (Nov. 29) 1932.

An infant aged 9 months became ill with fever, cough, diarrhea and restlessness, soon followed by convulsions and coma. At the first spinal puncture the fluid was clear; there were 490 lymphocytes per cubic millimeter, the sugar content was 84 mg. per hundred cubic centimeters, chlorides amounted to 7.76 Gm., and the globulin test was positive. No organisms were found on smear or culture. Nystagmus and facial paralysis developed after a few days. Instillation of spinal fluid into the previously scarified cornea of a rabbit and intracerebral inoculation of spinal fluid into a rabbit produced no obvious effect. The impression was that the infant had meningo-encephalitis due to a neurotropic ultramicroscopic virus.

LEMASTER, Evanston, Ill.

GOOD RESULTS FROM RADIOTHERAPY IN POLIOMYELITIS. S. GRACOSKI, Bull. Soc. de pediat. de Iasi **3**:122 (Nov. 29) 1932.

A child, aged 5½ years, suffered extensive paralysis of all four extremities and of the trunk muscles for four months following an acute attack of poliomyelitis. Marked improvement began immediately after roentgen irradiation of the spinal region was instituted. Treatments were given daily alternately to the lumbar and cervical part of the spine.

LEMASTER, Evanston, Ill.

VASCULAR CHANGES IN THE CENTRAL NERVOUS SYSTEM IN CHOREA RHEUMATICA. KALMAN V. SANTHA, Virchows Arch. f. path. Anat. **285**:405, 1932.

The brain of a 15 year old girl who suffered from a second attack of chorea and rheumatic carditis was examined histologically. The small vessels of the pia mater of the cerebral cortex showed extensive thrombosis, with organization and recanalization taking place in the oldest lesions. In the cortex of the brain numerous small areas of necrosis (infarcts) were found; it was remarkable that the basal ganglions were practically normal, though very slight thickening of the walls of the small vessels was observed. The parenchyma of the brain showed the lesions caused by the occlusion of the blood vessels. Occasionally, typical foci of encephalitis were found consisting chiefly of Hortega cells; no microorganisms could be detected in these lesions. The authors discuss the origin of the thrombotic process and, taking account of the changes in the intima which were observed, consider the changes in the blood vessels as the primary lesion which was a part of the general rheumatic involvement of the blood vessels.

SCHOENTHAL, New York.

ACUTE INFANTILE PARALYSIS; HEINE-MEDIN DISEASE. JOSEPH PELNÁŘ, Thomayer Lecture, no. 163, supp. Časop. lék. česk., Sept. 25, 1931.

Pelnář gives a complete historical sketch of acute anterior poliomyelitis and then comments on the clinical picture, diagnosis, prognosis, epidemiology, treatment and prophylaxis. The contemporary treatment is reviewed and evaluated. Con-

valescent serum seems to be of greatest value during the first stages of the disease, though Nobecourt reported death in a case in which the serum was given within thirty hours after the onset and before the appearance of any sign of paralysis. The spinalgia or spinal sign of Draper is considered valuable in differential diagnosis because it occurs very rarely in meningitis and polyneuritis.

STULIK, Chicago.

Diseases of the Eye

A PROCEDURE FOR THE EXTRACTION OF CONGENITAL, SOFT AND MEMBRANOUS CATARACTS. O. BARKAN, Am. J. Ophth. **15**:117 (Feb.) 1932.

Barkan reviews the various methods of operating on cataracts.

He suggests the use of epinephrine subconjunctivally to produce hypotony of the globe and maximum dilatation of the pupil. He also makes an oblique incision with a keratome 1 or 2 mm. from the limbus. This valvelike incision tends to close, especially when the pressure in the anterior chamber increases.

W. S. REESE. [ARCH. OPHTH.]

ACUTE INFLAMMATIONS OF THE ORBITS IN CHILDREN. R. C. GAMBLE, Arch. Ophth. **10**:483 (Oct.) 1933.

The terms by which orbital inflammations are described mean much from a surgical and pathologic standpoint, but the etiology is much more important in the matter of treatment. Such inflammation is usually the result of extension from the sinuses, but may be due to local injury or to embolic conditions such as scarlet fever. The frontal sinuses are not developed at birth and are not a factor in orbital disease in the first eight years of life. The ethmoid and the antral sinuses are present at birth. There is no proof that the lymphatics in the sinuses connect with those of the orbit, but there is a communication between the ethmoid veins and the superior ophthalmic vein. The intimate connection between the ethmoid and the antral sinuses and the orbit accounts for the relationship between disease of the sinuses and the orbit.

There are all grades of severity, even though the cause is the same. In the mild cases there are moderate redness and edema of the upper lid after disease of the upper respiratory tract. There is a greater discharge from the nostril on the same side. The eyeball becomes proptosed, pushed to one side and fixed. The cornea and optic nerve must be examined repeatedly. Subcutaneous induration either just above or below the internal canthal ligament is usually a sign of impending spontaneous rupture and may indicate when and where to open the abscess. Gamble believes that the process is really a subperiosteal abscess which pushes the periosteum away from the bone causing the proptosis and slowly burrows forward to break out under the skin, through the conjunctiva or backward to the apex of the orbit where it will cause serious trouble. When the pus appears beneath the conjunctiva the situation is more serious, because orbital and ocular tissues are then involved.

In many of these cases the condition is the result of an acute infection of a sinus, and Gamble believes that radical surgical procedures should be avoided. Pediatricians think that the treatment should be conservative because of metastatic foci of sepsis from such procedure. Ophthalmologists, realizing the danger to the ocular tissue, believe that an early and deep incision should be made into the orbit. Rhinologists think that it is wise to attack the seat of trouble. Gamble starts with tampons of epinephrine or ephedrine and mild silver protein in the nose and nasal suction. Cold applications are used in the early stages and hot in the later. If the abscess develops and points, it is opened without pressure and kept open. If there is not prompt improvement in the condition of the child and the proptosis, the rhinologist opens the ethmoid or the antral sinus.

WESCOTT, Chicago.

PARINAUD'S CONJUNCTIVITIS: CASE REPORT. THOMAS R. GAINES, J. South Carolina M. A. **29**:245 (Nov.) 1933.

Gaines reviews the literature on this unusual infection or disease and finds thirty-seven cases. His case is that of a school girl, 11 years of age. The involvement was in the upper lid of the left eye, with an enlargement of the preauricular and postauricular glands on the left side. In the history mention is made of six cats which were kept in the house in which the child lived. These cases are self-limited, and the treatment seems to be entirely symptomatic, the conjunctivitis clearing up in approximately three months' time. Parinaud described it as "a monocular conjunctival infection with follicle or granule formation, with involvement of the lymphatics on the affected side."

WESTON JR., Columbia, S. C.

Diseases of Ear, Nose and Throat

THE HYDROGEN ION CONCENTRATION OF NASAL SECRETION IN CHILDREN WITH ACUTE CORYZA. M. C. HILL and A. R. HARNES, J. Lab. & Clin. Med. **18**: 1029 (July) 1933.

In normal children the p_H of the nasal secretions was from 6.8 to 7.2, with a mean of 7.02 ± 0.021. In those with early acute coryza the p_H was from 7.2 to 7.9, with a mean of 7.69 ± 0.039. Thus, in the early stages of acute coryza the secretions show an alkaline reaction.

MCMURRAY, Galveston, Texas.

IDENTITY OF COURSE OF POSTTONSILLITIC SEPSIS AND PUERPERAL SEPSIS. F. A. SCHNEIDER, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **137**:75 (Nov. 24) 1933.

Schneider points out the similarity between posttonsillitic septicemia and puerperal sepsis in respect to etiology, pathogenesis, clinical course, complications and therapy. In both diseases the infection may spread by any of the following routes: the hematogenous, the lymphogenous, the lymphohematogenous and the perivascular, phlegmonous route. In both forms of sepsis there is the danger of pyemia, and metastases to the joints, kidneys, lungs and endocardium may occur. In both diseases the phlegmonous process tends to invade the large cavities of the body, causing peritonitis in puerperal infection and mediastinitis in posttonsillitic sepsis. Therapy in both forms of sepsis aims at elimination of the primary focus of infection, exposure of infected interstices and incision of peripheral abscesses. Ligation of veins in both diseases is indicated only in the event of thrombosis in a case in which the infection tends chiefly toward endophlebitic extension. The percentage of cures in severe cases in which surgical intervention is employed is about 50 per cent in both forms of sepsis.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

PULMONARY COMPLICATIONS AFTER TONSILLECTOMY. R. WALDAPFEL, Monatschr. f. Ohrenh. **68**:143 (Feb.) 1934.

Waldapfel, after a sojourn in the United States, was unable to explain the relative infrequency of abscesses of the lungs after tonsillectomy reported in Germany. He thought that it might be due to the superficial narcosis, with persistence of pharyngeal reflexes, and to the fact that the operation is performed with the patient in the sitting position. When patients showing posttonsillectomy fever were examined, however, he found eight with various pulmonary complications which had been absent before the operation. In making the diagnosis, roentgenography was the most important factor. In all these cases the prognosis was good. The prophylaxis of pulmonary complications of tonsillectomy consists in several measures. Narcosis should be as light as possible, so that the pharyngeal and cough reflexes are maintained. The operation should

be as short as possible. To reduce the infection of the blood stream, all possible asepsis of the oral cavity should be maintained. The author believes that the frequency of posttonsillectomy pulmonary complications in Germany is much greater than it was heretofore considered to be and that all patients showing fever after operation should be examined with this in mind.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

Surgery and Orthopedics

ABNORMALITIES OF THE VERTEBRAL BODY. WILLIAM A. EVANS, Am. J. Roentgenol. **27**:801 (June) 1932.

Improvement in roentgenology, with greater use of lateral views, has enhanced the value of roentgenology in the study of the vertebral column. The abnormalities may be grouped as: (1) chronological changes or normal variations peculiar to certain ages, (2) developmental anomalies, (3) changes associated with nutritional disorders like rickets, osteomalacia and familial osteochondrodystrophy, (4) changes resulting from trauma, both primary and secondary, (5) postural or occupational changes, (6) inflammatory changes like tuberculosis, syphilis, osteomyelitis, epiphysitis, osteochondritis and osteo-arthritis, (7) distortion of the bodies secondary to abnormalities of the intervertebral disks, (8) deformities caused by constitutional disease like those of the parathyroid gland and disturbances in lipoid metabolism and (9) deformities caused by malignant processes, both primary and metastatic. A bibliography and numerous roentgenograms are given.

STULIK, Chicago.

UNDESCENDED TESTICLE. CARL G. BURDICK and BRADLEY L. COLEY, Ann. Surg. **98**:495 (Oct.) 1933.

In a well illustrated article Burdick and Coley give in detail the operative technic and compare the end-results of Torek's operation with the discouraging end-results with former operative procedures.

The most suitable age for operation is between 8 and 12 years. The testis has thus had a chance to descend voluntarily, is larger and easier to manipulate and is placed in its normal position before the changes which come with puberty occur. If a large hernia accompanies the undescended testicle, earlier operation is indicated, since the use of a truss in this double condition is contraindicated.

The Torek operation consists of two stages. The first step is an incision as for inguinal hernia, and the testis is found and freed. An oblique incision is then made on the inner surface of the thigh at a site where the testis lies without undue tension, and the fascia lata is exposed. A pocket is made in the bottom of the scrotum, and the posterior lips of the two incisions are sutured together. The testis is then brought down through the scrotal wound and sutured to the fascia of the thigh. The anterior margins of the thigh and scrotal wounds are then sutured. The inguinal hernia is repaired in the usual manner, and the first stage is completed.

The second stage, releasing the testis from the thigh, is indicated as soon as the scrotum has stretched out to nearly the normal size, which is usually after two or three months. If this is not a convenient time, the second stage may be put off until the summer vacation with no apparent discomfort or disability to the patient.

BANTIN, Omaha.

PRINCIPLES VERSUS DETAILS IN THE TREATMENT OF ACUTE EMPYEMA. EVARTS A. GRAHAM and MAURICE BUCK, Ann. Surg. **98**:520 (Oct.) 1933.

Graham and Buck think that the whole question of the treatment of acute empyema has been confused by overemphasis on details of treatment, with a corresponding lack of emphasis on the underlying principles. The first object in the treatment of empyema is to save the life of the patient, and the second object is to shorten the period of convalescence as much as possible.

Several important facts are brought out: 1. Patients rarely, if ever, die of empyema itself. They die because of the complicating pneumonia, the presence of other severe complications such as abscesses of the brain, meningitis or peritonitis, or because an open drainage has been created at a time when such an open drainage produces fatal asphyxia. 2. If care is taken to avoid the creation of an open pneumothorax during the formative period of empyema, it makes practically no difference so far as mortality is concerned whether the condition is treated continuously by some form of closed drainage or by open drainage. 3. Nearly every case of acute pneumonia will reveal some fluid in the pleural cavity, if aspiration is performed. In most cases this fluid will be absorbed as the pneumonia clears, and statistics, based on recovery of such patients after aspiration, are often misleading. 4. The rate of mortality from acute empyema is governed almost entirely by the severity of the virulence of the epidemic.

BANTIN, Omaha.

ACUTE INTUSSUSCEPTION. EDWARD M. MILLER, Ann. Surg. **98**:706 (Oct.) 1933.

The majority of acute intussusceptions begin at or near the iliocecal valve, and 50 per cent occur in infants between the fifth and ninth month. The great number of cases during the early months of life are probably caused by abrupt changes in diet, cathartics, swallowed foreign bodies, abundant lymphoid tissue and long mesentery.

That method of treatment is best which, with the least amount of trauma and the least degree of shock, brings about complete reduction of the invaginated bowel, removes the local exciting cause and minimizes the likelihood of recurrence. Miller believes that in the early hours, especially with infants, conservative means, such as an enema given by the mother before the physician is called, gentle massage with the hand on the child's abdomen or gentle distention of the colon with warm water or barium sulphate water under the fluoroscope, may reduce the intussusception. However, the lack of knowledge as to the extent of the pathologic process and the uncertainty of the completeness of the reduction make immediate operation advisable.

BANTIN, Omaha.

APPENDICAL OXYURIASIS AND APPENDICITIS. HAROLD GORDON, Arch. Path. **16**:177 (Aug.) 1933.

Histologic examination of 26,051 appendixes removed surgically revealed oxyurids in 311, an incidence of 1.19 per cent. Amebas were found in 4 appendixes, Taenia saginata in 1 and Ascaris lumbricoides in 3. In 256 of the 311 cases of pinworms in the appendix, the parasites occurred in the lumen of the appendix without producing visible lesions. In 33 instances the oxyurids were found in the wall of the appendix, but since the evidence pointed in all cases to penetration after removal of the appendix, this type of invasion has no clinical significance. In 12 cases, minute mucosal lesions accompanied by punctate hemorrhages and a slight exudation and necrosis were caused by the pinworms. In view of this study the author concludes that Oxyuris vermicularis is not a significant cause of appendical pathologic changes.

LEMASTER, Evanston, Ill.

THE CHOICE OF TREATMENT IN ACUTE EMPYEMA. CARL EGGERS, New York State J. Med. **33**:145 (Feb. 1) 1933.

The article is a discussion of aspiration, closed methods of drainage and open methods of drainage in the treatment of empyema.

AIKMAN, Rochester, N. Y.

FURTHER EXPERIENCES IN THE TREATMENT OF EMPYEMA THORACIS BY PACKING. JOHN F. CONNORS, New York State J. Med. **33**:149 (Feb. 1) 1933.

The cases of twenty-three patients with empyema who were treated by packing the pleural cavity with gauze are reported. Seven of the patients were under 10

years of age. A previous series of thirty-five cases was reported in 1931. Unless the disease is advancing, surgical intervention is postponed until the patient's general condition is improved. A special group has performed the operations in these cases at the Harlem Hospital.

After removing about 2½ inches (6 cm.) from adjacent ribs, a hole about 2 inches (5 cm.) in diameter is made in the chest. Through this the operator can investigate adhesions and pockets of pus by means of the Cameron lamp. After the pus is removed the pleural cavity is packed with gauze, which is removed in two days. The hole in the chest is kept open until the lung has completely expanded. Two of the twenty-three patients died. The advantages of the method are cited.

AIKMAN, Rochester, N. Y.

PURULENT PLEURISY IN CHILDREN. G. RATICHVILI, Arch. de méd. d. enf. **36**: 606 (Oct.) 1933.

The author discusses the usual methods of evacuating purulent exudates in the pleural cavity, based on the management of 170 cases in young persons. In this series there was, as usual, a great preponderance of males, and the left side of the thorax was affected much more frequently than the right. Eighty per cent of the infections developed in the cold months. In the treatment of these empyemas, simple thoracotomy was practiced in 142 and resection in 17, while repeated puncture was employed in 11. There was the same mortality among the patients treated by the first two methods (30 per cent), and only 18 per cent among those having multiple aspiration. It is pointed out, however, that these figures do not take into account the age of the patient, the preceding type of pneumonia and the coexisting complications.

Although the death rate still reaches startling figures, it is refreshing to compare the present mortality with that of a century ago, when Dupuytren, the famous French surgeon, refused surgical intervention for empyema with the remark that he had rather die at the hand of God than that of a doctor!

AMESSE, Denver.

OPEN REDUCTION OF CONGENITAL DISLOCATIONS OF THE HIP. MUTEL, Rev. d'orthop. **20**:385 (Sept.-Oct.) 1933.

The author gives a complete review of the various methods for reduction of congenital dislocations of the hip. The subject is thoroughly discussed, including the (1) obstacles to closed and open reduction, (2) methods of overcoming these obstructions and (3) methods of operation of various authorities, including Lane, Kidner, Groves and Bade.

If reduction is attempted early, closed methods will give satisfactory results in approximately 75 per cent of cases. When closed reduction has not produced results, open reduction should be resorted to. In very young patients, the simpler operations, such as that proposed by Kidner, will overcome the obstacles to reduction. In older children, tenotomies or even osteotomies, may be necessary in addition. The majority of authorities quoted place the age limits to satisfactory results of surgical intervention between 2 and 10 years. Under 2, the bony framework is not sufficiently developed to permit intervention, and after 10, the obstacles to successful treatment increase. An excellent bibliography is given.

RYAN, Vancouver, B. C.

TWELVE HUNDRED APPENDECTOMIES IN EASTERN EUROPE. I. PHILIPOWICZ and T. HNIDEI, Beitr. z. klin. Chir. **156**:285, 1932.

Whereas before and soon after the World War there were comparatively few cases of acute appendicitis, since then until the present time there has been a great increase in numbers. The question is brought up if the change in diet

among eastern Europeans has anything to do with this factor, that is, the ingestion of more meat than vegetables. Does this change cause the disappearance of normal colon bacilli and the replacement by pathogenic anaerobes? RUBIN, Boston.

RESULTS OF HERNIOTOMIES IN CHILDREN. H. MARXER, Beitr. z. klin. Chir. **156**: 521, 1932.

Marxer's experience in forty-three cases shows that excision of the hernial sac surely prevents postoperative damage such as atrophy of the testicle or relapse. He believes that there should be no fear of operating on children.

RUBIN, Boston.

THE BEGINNING OF SO-CALLED COXA VARA CONGENITA. K. GÜTIG and A. HERZOG, Beitr. z. klin. Chir. **156**:551, 1932.

Gütig and Herzog emphatically state that they do not believe coxa vara to be of congenital origin. It begins with a destructive focus in the neck of the femur just distal to the epiphyseal line. It does not involve the epiphysis. They call it aseptic necrosis of the neck of the femur. The resultant coxa vara depends on the amount of destruction.

RUBIN, Boston.

THERAPEUTIC EXPERIENCE IN PLEURAL EMPYEMA IN CHILDHOOD. GUNTHER PASCHLAU and ERNST LEHMAN, Klin. Wchnschr. **10**:542 (March 21) 1931.

The authors give their experience with 137 patients. They point out that, in general, deaths should not be considered a criterion of the therapeutic method, since death, especially in infants, is due to the pneumonia rather than to the empyema. They consider treatment by puncture to be the choice during the first year. Nearly 30 per cent of 58 patients recovered under treatment by this method alone. Occasionally a patient recovered with one or two punctures, but more often from three to eight were necessary; 1 infant recovered after thirty punctures, but obviously this is not the likely result when so many become necessary. Small encapsulated empyemas or larger ones in which the temperature has become normal are more likely to yield to this method alone. Half the patients had to have other procedures. Puncture should be given up when it becomes difficult to withdraw the pus or when an infection of the wall of the chest takes place. Closed drainage in which continuous suction was used (Heber drainage) was employed in 37 cases. This method provides better and more complete emptying than do punctures. In this group, resection became necessary in 7 patients. Collapse did not occur in any of the cases, and pneumothorax, when it did occur, was of minor significance. Erosion of the rib occurred three times. Paschlau and Lehman consider narrow intercostal spaces as a contraindication.

Resection was done in 43 cases, and in 28 as a secondary procedure. The hesitancy to use this method is due to the acute changes in pressure with the accompanying changes in the respiration and circulation as well as the flutter of the mediastinum and postoperative collapse. The authors consider resection best employed as a secondary operation, puncture or closed drainage being used first. Resection should not be done until the second week of the empyema; it should not be done while the pneumonia persists. Closed, continuous drainage is the method of choice. It is believed that the initial puncture should be delayed until it is absolutely necessary, and that subsequent punctures should be repeated only when the respiratory embarrassment again becomes evident.

SILVERMAN, Syracuse. N. Y.

GALLSTONES IN EARLY CHILDHOOD. FRIEDRICH ECKARDT, Monatschr. f. Kinderh. **58**:352, 1933.

To three cases already reported in the literature, the writer adds another. Gallstones were an incidental finding in an autopsy done on a child dying of meningitis.

GERSTLEY, Chicago.

Miscellaneous

THE RELATION BETWEEN NUTRITION, MENTAL LEVEL AND ADUSTMENT IN DELINQUENT BOYS. MATHEW MOLITCH and AUGUSTUS H. ECCLES, J. Nerv. & Ment. Dis. **78**:234 (Aug.) 1933.

The nutrition index used in this study is based on the width-height ratio, this being a more logical clue to the nutritional status than is offered by the age-weight-height relationship. Eight hundred boys between the ages of 8 and 18 years were studied in the New Jersey State Home for Boys. In approximating the mental level, different recognized tests were used to discover general as well as special adaptability. The rating for behavior of each boy was secured from the cottage father and was patterned according to the Vineland Adjustment Score Card, conduct being scored on the basis of social values. Following is part of the summary:

From the psychologic standpoint, a study of 554 cases revealed no significant differences in general mental level or overt behavior between the boys who were well nourished and those who were undernourished. However, the undernourished group exhibited a shade of disadvantage in both mentality and the quality of social adjustment. Generally, the delinquent boy is not the undernourished boy.

JAHR, Omaha.

GENERAL CONSIDERATIONS ON THE TEMPORARY DECIDUOUS TEETH. MATEU CEBRIA, Paidoterapia **12**:669 (Nov.) 1933.

The deciduous teeth have not only masticatory function during the early years, but also that of guiding and favoring the development and eruption of the permanent teeth.

The origin of the permanent teeth is a normal physiologic process, but in certain cases the teeth appear in an abnormal manner. Therefore, it is absolutely necessary to watch closely the evolution of the permanent teeth by instituting an efficient prophylaxis of dentition troubles in the deciduous teeth and continuing this prophylaxis until the permanent teeth are all present.

HERRON, Spokane, Wash.

THE SURROUNDINGS (MILIEU) OF THE CHILD AND THEIR RELATION TO SOCIAL SERVICE. A. BUSEMANN, Gesundhfürs. f. d. Kindesalt. **8**:157 (Aug.) 1933.

The author discusses the influences on the child during development and demonstrates how they exaggerate the pernicious tendencies of inheritance. The new movement in Germany emphasizes the protection of the family as well as the elimination of the unfit through sterilization.

REICHLE, Cleveland.

LIFE OF THE CHILD IN THE FAMILY AND IN AN INSTITUTION. H. HETZER, Gesundhfürs. f. d. Kindesalt. **8**:164 (Aug.) 1933.

The child's proper habitat is the home. Its limitations are recognized, but the dangers of "hospitalization" are considerably greater. The Soviet ideal of collective education is being abandoned in Central Europe.

REICHLE, Cleveland.

THE TURNTABLE: A HISTORICAL STUDY. R. FISCHL, Gesundhfürs. f. d. Kindesalt. **8**:220 (Aug.) 1933.

The famous Austrian pediatrician presents an interesting study of the illegitimate child, its social importance and its treatment by the people of the ancient and the modern world. He describes the turntable, which was first used in the Middle Ages (1198) for the deposition of illegitimate or abandoned children in monasteries and which is still used in Spain and Brazil.

REICHLE, Cleveland.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Regular Meeting, March 20, 1934

CHARLES SCHOTT, M.D., *President, Presiding*

SCARLATINIFORM RASH WITH HEMOLYTIC STAPHYLOCOCCIC INFECTION OF THE THROAT. DR. JOHN S. MCDAVID.

Recently I was called to see a girl 8 years old. She was vomiting and had a temperature of 102 F. and a scarlatiniform rash. Her throat was much inflamed and was probably of a deeper red than is usual in scarlet fever. The inflammation was closely confined to the tonsils and the posterior pharyngeal wall. There was no marked redness of the soft palate or uvula. The rash was of the diffuse erythematous type associated with scarlet fever, except for the fact that the cutaneous papillae were more prominent than usual, giving the skin a more roughened appearance. The lower part of the abdomen was completely covered by the rash, which dipped down into the creases of the skin in the manner associated with scarlet fever. The thorax showed only patchy areas here and there, with areas of normal skin between. The left arm and hand was entirely covered, and little normal skin could be seen on the right forearm and hand.

To be more certain of the diagnosis, a blood agar culture was made from the throat and incubated at 37 C. There was a profuse growth of hemolytic organisms, but the colonies did not look like those of streptococci, and they proved to be those of hemolytic staphylococci. This growth was subcultured twice, and later cultures from the throat also showed only hemolytic staphylococci. The bacteria soon lost their tendency to hemolysis on subcultures.

One week after the child was first seen the skin began to exfoliate extensively over her hands, forearms and abdomen. There were no complications, and she was back in school two weeks after the onset of the illness.

There are a few very interesting side-lights on this case. Five months previous to the infection, she had been given the Dick test, the result of which was markedly positive. The mother said that the skin over the area of the test exfoliated, and that the discolored area was approximately the size of a half dollar. The rash described did not invade this area, although it was present around it.

The Dick test was carried out on the opposite arm three weeks after the onset of the illness and the result was negative. The reaction was again negative when the test was repeated five weeks later.

Dr. C. C. O'Kell, bacteriologist of the University College Hospital in London, has repeatedly called attention to the clinical similarity of the exotoxins of hemolytic organisms. He believes that the rash of scarlet fever is simply an exhibition of the fact that in this particular strain of hemolytic streptococcus an enormous amount of exotoxin develops. Gustave Neuhauser and several other authors have shown that children convalescing from diseases other than scarlet fever show a much higher percentage of negative reactions to the Dick test than normal adults.

This case seems to be one in which a known positive reaction to the Dick test changed to a negative one with an infection other than scarlet fever. According to the history given by the parents, this child was never ill from the time of her first positive Dick reaction until this illness.

DISCUSSION

Dr. M. L. Blatt: The decision as to what clinical syndrome in atypical cases constitutes scarlet fever is subject to the point of view of the diagnostician.

This morning I went into my ward at the Cook County Hospital and saw a number of children ill with diseases that looked like sequelae of scarlet fever. A child with hemorrhagic nephritis without the history or clinical symptoms of scarlet fever, with no peeling and with hemolytic streptococci predominant in the culture from the throat, presented one of the puzzling cases. Another child had purulent otitis media and swollen glands. The tongue looked like that of a patient with scarlet fever. There was no history of vomiting at the onset, and there had been no erythema. Is this scarlet fever? I have believed for many years that two organs are of great importance in the production of immunity: the liver and the skin. It seems probable that the erythema of scarlet fever is a physiologic response to the toxin of scarlet fever. I believe that the erythemas of the exanthems of infectious disease represent the physiologic reactivity of the skin to a hemolytic toxin such as Dr. McDavid described. The Dick reaction is the same picture localized. In my experience, the Dick reaction has seemed specific, but a negative reaction may become positive without apparent cause. Patients frequently show an erythematous reaction following prophylactic administration of the Dick toxin, yet this is not scarlet fever, nor is the condition in Dr. McDavid's case.

Dr. Archibald Hoyne: In accordance with the ideas now prevalent, one would not be justified in admitting that the case reported by Dr. McDavid was one of scarlet fever. The only similar case I have seen that I know was due to hemolytic staphylococci was that of a child, who died; hemolytic staphylococci were found in the blood. The condition closely resembled hemorrhagic smallpox, with which it had been confused. If scarlet fever is due to hemolytic streptococci, one cannot admit that this case was one of scarlet fever. Why the Dick reaction should have changed is difficult to understand.

Dr. F. W. Schlutz: I recall an article written a great many years ago by a Hungarian investigator, in which he mentioned the fact that probably many of the toxic rashes, particularly the rash in scarlet fever, occur in persons who are allergic to certain toxins. Hemolytic streptococci or staphylococci can be cultured from the blood of persons without any rash; yet a person who is allergic shows his symptoms in the form of a rash.

Dr. George F. Munns: Two months ago I saw an 11 year old boy who, for the third time in my knowledge, had a generalized erythematous rash following an infection of the skin. With the third rash there were a great many petechiae on the chest and a few scattered on other parts of the body. The boy was not seriously ill with the first two infections, but in this instance he had staphylococcic septicemia, osteomyelitis of each tibia, a purulent infection of the left hip joint, bronchial pneumonia and pleurisy with effusion. Hemolytic staphylococci were recovered from each lesion. The patient survived the infection and is making a slow recovery.

The Management of the Rheumatic Child. Dr. Robert Black.

I am not saying anything new when I speak of the close resemblance of rheumatism to tuberculosis. Both diseases may be latent and may make a sudden dramatic appearance, and in both months may be required before a definite diagnosis can be made. In young persons tuberculosis and rheumatism both assume a generalized form. Later, with age, both tend to become localized, tuberculosis as a chronic fibrous condition of the lungs and rheumatism as mitral stenosis of a fibrous nature. In both diseases there are chronicity, a tendency to relapse and a low intermittent temperature. Both conditions become progressively worse, unless properly handled. The physician specializing in tuberculosis speaks of an arrested condition, rarely of a cure. So I speak only of arrested rheumatism.

Unless unusual care is taken, 30 per cent of rheumatic children will suffer relapse, with a definite second attack within eighteen months. Few are without a relapse of more or less severity.

The rheumatic child should receive the same management that the tuberculous child receives. The parent should be trained to take the position that all discipline should not be relaxed merely because the child is nervous and has a heart murmur. I know of no quicker way to send the child with cardiac disease to the grave than to spoil him. Equally important is the education of the child without making him conscious that he is an invalid or a crippled child. He should be trained to rest when tired.

In the management, alertness as to reinfection or recrudescence is of first importance. If a child who has recently recovered from an acute attack of rheumatism shows, on account of overexercise, even without a new infection, the same group of symptoms—malaise, increasing irritability, fickle appetite, increasing pulse rate, rise in temperature, pallor and fatigue—one is facing a relapse. Night sweating or afternoon sweating is a marked symptom and often precedes all others. This symptom is one which the physician often fails to impress on the nurse or the mother as one to be on the alert for. The pulse rate is hard to evaluate in these highly nervous children, and frequently it is better taken by the mother or the nurse than by the physician.

Keeping the child in bed is of prime importance, and the patients soon learn to be happy and to enjoy working with the head and hands and not the entire body. The difficulty is to know when to let the child out of bed; as yet no method has been evolved except through experience. Our method is, first, to allow bathroom privileges, then to allow the patient to remain up for one hour, then for two, three and four hours, etc. As a rule, before the child is given bathroom privileges he has already had considerable exercise in bed.

In my experience, warmth has much to do with the condition of the child, and, while every effort is made to keep the air fresh, cold air is avoided.

The nutrition of the rheumatic child furnishes a problem. The most successful plan has been to start with small quantities of food on the tray and to demand that the tray be cleared before going to bed or participating in play or amusement. This rule is enforced until it becomes a habit. Then the amounts of food on the tray are gradually increased. After trying all methods of fortifying the milk in order to increase the calories taken, it was finally found that dry milk is the best. From 4 to 12 tablespoonfuls to a quart of milk (from 60 to 180 cc. to 946 cc.) is used. It is well tolerated, and the child acquires a liking for it instead of growing tired of it.

In the way of medicine, cod liver oil, iron and other drugs have a place, when needed, but I have long had a preference for sodium salicylate in large doses, given by rectum for from three to five days, then in much smaller dosage by mouth. Although I have used this method for the past ten years, with no bad results, I have had, within the last three months, toxic results in three cases. These three cases all occurred within one month. The use of various vaccines or foreign proteins is of help and probably should be tried more often, but the increased temperature and pulse rate sometimes cause the physician anxiety.

DISCUSSION

DR. STANLEY GIBSON: Dr. Black has outlined very well the essentials of management of the rheumatic child. All physicians recognize the great importance of long-continued rest. To know when infection has subsided is difficult. One must consider the temperature, the blood count, the weight curve, the turgor of the skin and, finally, the general appearance. I seldom allow a child to be up without consulting the head nurse. She is in the ward constantly, is alert, observes all the aches and pains of the children and is often in a better position to say when the child should be up than the physician, who sees the patient for only a few minutes every day or so.

Once the child is convalescent it is important that he have a moderate amount of activity and not be made to believe that he is a cardiac cripple. A great many

of the children can engage in most childhood activities, yet are constantly nagged by the parents in the effort to prevent them from doing too much. The rheumatic child should have special care and more rest than the normal child, but he should not be made miserable by being reminded repeatedly of his ailment.

DR. ARTHUR H. PARMELEE: This paper is important and timely. Rheumatic fever, with its effect on the heart, stands at or near the top among the causes of death in children of school age in this part of the country, and it is strange that it has received so little attention in the deliberations of this society. Dr. Black's remarks about the treatment of rheumatic fever with massive doses of salicylates interest me. I have used this method on several occasions and believe that it has definite advantages. But the symptoms sometimes encountered as a result of this form of treatment are alarming unless one is expecting them. The rapid respiratory rate and slight cyanosis make the patient appear quite ill, but these symptoms subside rapidly when the salicylates are omitted or when the dosage is radically reduced.

The relief from pain is important in the treatment. The best results are obtained when salicylates are given at regular intervals throughout the twenty-four hours.

In deciding when to allow the patient to be up and how much restriction shall be put on physical activity, the psychic as well as the physical results must be taken into consideration. I am inclined in some cases to take a chance on the the physical consequences in order to avoid mental invalidism.

DR. F. W. SCHLUTZ: I wish to ask Dr. Black what his attitude is regarding tonsillectomy in cases in which there are recurrent relapses. I have the impression that we physicians are often too conservative in that respect. The case which he described is, I think, a good illustration. It has been my experience that it is safe to be somewhat radical and not too fearful in cases in which there are continued relapses. One often saves a patient whom one would probably lose if one did not proceed with such an operation at a favorable time.

With reference to the decision as to when to allow the child to be up, I am more and more impressed with the value of the sedimentation rate along with other symptoms that indicate a favorable condition of the child, such as a more normal pulse rate and a better state of nutrition. It has been my experience in the children I have had under my care for several years that a favorable change in the sedimentation rate is a good index of the amount of activity to be allowed these children, and I think that increasing clinical evidence will support this view.

DR. H. WILLIAM ELGHAMMER: In considering the question of when to allow the child to be up, there seem to be two main problems: first, the activity of the rheumatic infection and, second, the capacity of the heart. My associates and I thought at first that by using some method of testing the capacity of the heart we should find the solution, but the further we went into this the more we found that it was of little value in determining the opportune time for the child to resume exercise. In contrast to our experience with the adult, we have failed to see cardiac decompensation in the child from mechanical factors. This may occur, but we have found it to be due to an active infectious process. Any infection in the human body alters the blood stream, that is, the component parts of the blood plasma and the albumin-globulin ratio. A precipitation test has been devised which gives an index of the presence of toxic substances in the blood plasma. I reported last month our experience with the sedimentation test in chronic rheumatic infection. We found, as Dr. Schlutz pointed out, that this test is of definite value in determining the activity and severity of the rheumatic infection. So far we have had no reason to regret our trust in the sedimentation test.

DR. H. G. PONCHER: I should like to know how Dr. Black regards the contagiousness of the rheumatic infection, whether there is any difficulty in putting patients in a room together and whether any active infection results from this.

DR. JAMES H. WALLACE: To carry Dr. Black's analogy between tuberculosis and rheumatism further and with bearing on the treatment of the convalescent

child, the virtue of the dry, hot Southwest comes to mind. Apparently, rheumatism is practically nonexistent in Arizona and New Mexico, and there is an increased analogy in that rheumatic patients are greatly benefited by the climate there, just as patients with tuberculosis are. Probably this is a field that should be exploited.

DR. THOMAS P. SALTIEL: I wish to know Dr. Black's opinion in regard to treatment with acetylsalicylic acid instead of salicylates and whether there is a toxic reaction from the former.

DR. ROBERT BLACK: I am glad that Dr. Gibson brought out the oversolicitude regarding the activity of the child with rheumatism. I have tried to get around this by limiting the time of exercise, letting the child do anything he pleases so long as he does not do it too long. When one does let him go, one should let him go his normal gait, but limit the time. It is the long pull rather than the short flurry that counts.

I wish to justify Dr. Jampolis' opinion in regard to the removal of the tonsils. They were never in shape to take out, and before they could be removed there would be another acute flare-up. Two or three times I have taken tonsils out when there was great hesitancy about doing so, and perhaps I sometimes leaned the other way, although I have taken out tonsils in a great many rheumatic children when the tonsils were apparently diseased or when the children were absorbing enough toxin to harm them.

I am glad to verify Dr. Elghammer's remarks about the sedimentation rate, which I have found satisfactory in my work.

I am also glad to confirm Dr. Gibson's statement that in rheumatic children one does not often see relapses from a mechanical cause but does from an infectious cause. I tried to bring out that the old rheumatic heart seems to acquire an immunity to fever, and that if one takes fever as a sign of relapse one will be rather badly fooled.

As to contagiousness, I am not prepared to say anything about that. There has been no evidence to lead me to believe that the condition is contagious.

As to acetylsalicylic acid and salicylates, I think that the former relieves the pain perhaps a little better than the latter. I was surprised to learn that the English use acetylsalicylic acid more than the physicians in this country do, 10 grains (0.6 Gm.) not being considered a large dose. I am glad to have Dr. Parmelee indorse giving large doses of salicylates. I give as much as from 20 to 60 grains (1.3 to 3.8 Gm.) three times a day by rectum, and after using the drug for ten years I am ashamed to acknowledge that the first case of salicylate poisoning which I saw I did not recognize. For the benefit of those who have not seen a case of sodium salicylate poisoning, I wish to say that it is a rather startling experience.

The opinion was expressed that advance in the treatment of rheumatic fever will not be made until the cause is found. I do not think that the physicians specializing in tuberculosis made much advance after they found the cause of that disease. I brought out the point in regard to tuberculosis because I thought that the parallelism was so great that one could see the advantage of taking care of rheumatic children in a like manner. I stressed in the paper that in my opinion infection is the secret of the whole thing.

Dr. Wallace is right about the hot, dry Southwest. There is little rheumatism there, very little in Florida and very little in Porto Rico. Some of the pediatricians in New York have established camps in Florida and in Cuba and have been sending rheumatic children there. These camps have been established for the past four or five years. It has been definitely concluded that if patients go to Puerto Rico for a cure they had better remain there for two or three years, for in a great percentage a relapse occurs during the winter following their return to the northern climate.

II. The Calcium and Phosphorus Content of the Offspring After Feeding Vitamin D to the Mother Rat. Dr. W. W. Swanson and Dr. L. V. Iob.

This article will be published in full in a later issue of the American Journal of Diseases of Children.

Diphtheritic Myocarditis: A Review of 496 Cases (Inaugural Thesis). Dr. Archibald Hoyne and Dr. Norman T. Welford.

Because of the importance of diphtheritic myocarditis we determined to make a study of all the cases of diphtheria under treatment in the Municipal Contagious Disease Hospital during the period from 1928 to 1932 in which a diagnosis of myocarditis was definitely established. During the quinquennium referred to 4,671 patients with diphtheria were admitted; among these there were 548 deaths, or a fatality rate of 11 per cent. Myocarditis was definitely demonstrated as a complication in 496 instances, or 10.6 per cent of all the cases. It was the latter group that we undertook to analyze.

Little difference was noted in the frequency with which myocarditis occurred in the sexes, there having been 250 males and 246 females. On the other hand, contrary to the experience of some observers, the fatality rate was higher among the males, being 67 per cent, as compared with 55 per cent for the females. One of us has previously called attention to the apparent fact that the Negro is less susceptible to diphtheria than the white person, and we found this view upheld among the 496 cases of myocarditis, of which but 28 (5 per cent) were in Negroes.

The highest mortality occurred in those who were 5 years of age or younger. Frequency and mortality were next greatest in the second five year period, while patients older than 15 years of age suffered the least.

The tonsillar cases, in which the absorption of toxin from the site of the membrane was least rapid, showed the lowest death rate, whereas those with nasal involvement showed the greatest number of fatal terminations and also the highest percentage of deaths, if one excludes the tracheobronchial cases, in which the unfavorable outcome was primarily due to asphyxia.

Of the deaths due to myocarditis, 79 per cent occurred within the first two weeks of the illness, while 21 per cent occurred later. The period during which the development of myocarditis in the average case of diphtheria is to be most feared is from the tenth to the fourteenth day of the disease.

The amount of antitoxin administered varied according to the location and extent of the membranous lesions. As a rule, 50,000 units was the maximum dose used. This amount was reserved for cases in which an extensive membrane covered the tonsils, uvula, pharynx and nasal mucosa. Patients with simple tonsillar diphtheria received from 10,000 to 20,000 units. Patients with nasal involvement never received less than 20,000 units, and frequently 40,000 units was administered. The results obtained from these moderate dosages seemed in every way more satisfactory than those from large doses. In severely toxic cases, 10,000 units of antitoxin was administered intravenously, while the remainder was given intramuscularly.

One hundred and twelve patients presenting grave symptoms of diphtheritic myocarditis were given repeated intravenous or intramuscular injections of a 10 per cent solution of dextrose. In children under 5 years of age the intramuscular route was substituted for the intravenous route. The amount of each injection varied from 100 to 200 cc. Each patient received from two to nine injections. The treatment was not used in mild or moderately severe cases. The patients to whom dextrose was administered were all critically ill and in some instances almost moribund.

Of the 112 patients treated with dextrose, 10 recovered. One might question the efficacy of any form of treatment in which there was a recovery rate of only 9 per cent. Yet, considering that we were dealing with a group of cases that had already been referred to as cases of malignant diphtheria, we believe that the

dextrose therapy was not entirely in vain. Owing to the severity of these cases, death would probably have supervened in practically every instance, had not dextrose been administered.

Coincident with our study of dextrose therapy, blood sugar determinations were made in 29 cases of severe diphtheritic myocarditis, 55 estimations being made in all. The first blood sugar determination on each patient was made during fasting, and the second was made at varying intervals after the intravenous or intramuscular injection of dextrose. Eleven cases showed a fasting blood sugar level above 120 mg. The remaining 18 cases showed a blood sugar level within normal limits. Fasting blood sugar values ranged from 80 mg. to 152 mg. per hundred cubic centimeters, the average being 110 mg. Following the intravenous or intramuscular injection of dextrose, there was a definite and sharp rise in the blood sugar, the average increase being 40 mg. per hundred cubic centimeters.

If there was a decreased output of insulin in these cases, the use of dextrose with insulin in the treatment suggested itself. Favorable results from the use of dextrose-insulin therapy have been reported by several investigators within the last two or three years.

So far the number of cases in which treatment with dextrose or with dextrose and insulin was tried has been too small to permit any fully developed conclusions regarding the value of such therapy in severe diphtheritic myocarditis. Nevertheless, the results seem sufficiently favorable to justify the use of dextrose intravenously or intramuscularly in every severe case of myocarditis due to diphtheria.

DISCUSSION

DR. ARCHIBALD HOYNE: Sixteen years ago, in March, I read a paper before this society dealing with mortality in diphtheria. The signs of impending myocarditis in diphtheria have not changed in all those years. The signs that have been emphasized—the drop in pulse rate, nausea, vomiting and abdominal pain—frequently appear before there are any definite cardiac signs, and if these are accompanied by albuminuria the prognosis is extremely bad. Physicians used to believe that if the patient had only abdominal pain and nausea he had a fair chance to recover, but that if vomiting occurred he would die, and it is seldom that this is not correct. In spite of all the time that has elapsed and all that has been done in the study of diphtheria in connection with the heart, not much advance has been made, aside from the treatment with dextrose. Next to diphtheria antitoxin, the most important thing is rest, but I think that some patients who receive dextrose survive who would die without it.

DR. GEORGE F. MUNNS: Epinephrine hydrochloride is useful in the treatment of patients with diphtheritic myocarditis, and it is known that epinephrine has a great deal to do with the glycogen and sugar metabolism of the body. Possibly it acts on the heart not only directly but through an effect on the dextrose metabolism.

DR. JESSE R. GERSTLEY: Did Dr. Welford have an opportunity to try oxygen therapy, and, if so, what were the results?

DR. ABE MATHESON: I wish to know the authors' experience as to the incidence of mural thrombosis and embolism in their series of cases.

DR. HAROLD ROTHBART: Were any changes of the vagus nerve noted pathologically?

DR. STANLEY GIBSON: When are these patients out of danger? Does sudden death occur after the acute change has apparently passed?

DR. JAMES H. WALLACE: I should like to find out what has happened to these hearts five years after the acute myocarditis—what aftermath they may show in signs of heart disease.

DR. NORMAN T. WELFORD: Regarding carbohydrate metabolism as a factor in circulatory failure in diphtheria, investigators at Johns Hopkins University

School of Medicine have done some work and have gone so far as to say that disturbance of carbohydrate metabolism may be the most important factor in circulatory failure in these cases.

As to pathologic observations in this group of cases, we believe that sufficient pathologic evidence was present to account for every case on the basis of myocarditis. None of the patients was given oxygen therapy. We saw embolism and thrombosis occasionally at necropsy, but I am not able to state with what frequency. It has been definitely disproved that changes in the vagus are the cause of death in such cases. Warthin, in a comprehensive review of the pathologic observations over a long period, stated that the vagus has little to do with death in cases of diphtheritic myocarditis.

As to the time when these patients are entirely out of danger, they are kept flat on their backs for several weeks, and usually are discharged from the hospital after five or six weeks, to continue rest at home. Since the hospital is not equipped with an electrocardiograph, we are unable to follow up the patients and find when they have entirely recovered from myocarditis. However, judging from reports of follow-up investigations in cases of diphtheritic myocarditis, practically all the patients make a complete recovery.

DR. ARCHIBALD HOYNE: Diphtheria is at its lowest ebb in Chicago, but that is not sufficient ground for looking on this subject as untimely. Only a few years ago diphtheria showed a marked increase in some foreign cities: Düsseldorf, Leeds and many other places. Physicians there are of the opinion that the disease is becoming worse; and unless immunization is carried out continuously there is no reason why a rebound may not occur, and then we will have some of it here.

Regular Meeting, April 17, 1934

CHARLES SCHOTT, M.D., *President, Presiding*

AMEBIC DYSENTERY. DR. M. H. STREICHER (by invitation).

This boy was about 7 years old when he was first seen, and is now about 8. On April 18, 1933, he was taken to the Sarah Morris Memorial Ward of the Michael Reese Hospital, with chills, fever, diarrhea, blood and pus in the stools and moderate loss of weight. He remained in the hospital until August 30. During that time he was under the care of a capable pediatrician connected with that hospital. Examination of the stools showed Shiga's bacillus. No amebae were found in the stools on several examinations.

I saw the patient first on April 26, when proctoscopic examination revealed ulcerated lesions of the colon, which I thought were due to a mixed infection. Treatment for bacillary dysentery of the Shiga type was continued by the pediatrician. I saw the child again on August 30, when he had been sent home from the hospital after examination of the stools gave negative results.

Almost immediately on his return home I started treatment for amebic dysentery for the first time. He had a septic temperature throughout the course, ranging from 105 F. (p. m.) to 96.5 F. (a. m.). In October he showed a severe reaction. The liver was about five fingerbreadths below the normal level of the border. He was taken to Grant Hospital on October 18.

I operated on him on October 21, expecting to find a solitary abscess of the liver, but found multiple suppurative cholangeitis. I opened the gallbladder and drained it for four weeks. The liver shrank gradually, and the child gained weight on treatment for amebic dysentery: His weight last summer was 26 pounds (11.8 Kg.); he now weighs 48 pounds (21.8 Kg.). He still has an enlarged liver, but it has shrunken considerably. I am presenting a roentgenogram showing the edge of the liver extending down to the crest of the ilium and another showing a typical picture of a colon in which the ulcerative process is far advanced.

Four positive cultures of the stools showing encysted forms were reported about six and a half months after treatment for amebic dysentery was instituted. At present six of nine stools, according to reports from the city laboratory and our own laboratory at Grant Hospital, show no amebae. The patient now has one stool a day and is up and about, being out of bed for the first time in eighteen months. He attends movies regularly.

DISCUSSION

A question was asked in regard to the nature of the treatment.

DR. M. H. STREICHER: We gave emetine bismuth iodide by mouth; the treatment varied as the clinical course changed. We also used chiniofon in variable dosages.

We gave emetine bismuth iodide for ten successive days and then examined the stools for three days. A period of rest was allowed; the treatment was repeated, and the stools were examined. Emetine hydrochloride is not used in the chronic stage or the carrier stage. In the treatment it is also important to supply fluids by hypodermoclysis in the form of saline solution and 5 per cent dextrose.

DR. H. E. IRISH: Did you regard this as bacillary dysentery of the Shiga type plus amebic dysentery or as primary amebic dysentery?

DR. M. H. STREICHER: On account of the child's age, I should, of course, consider bacillary dysentery of the Shiga type, but often these conditions are mixed infections. After a child has been ill for from six to nine months, treatment for bacillary dysentery of the Shiga type is purely symptomatic. Therefore, we considered this condition amebic dysentery complicated by abscess of the liver.

THE INFLUENCE OF BREAST AND ARTIFICIAL FEEDING ON THE MORBIDITY AND MORTALITY OF 20,000 INFANTS. DR. CLIFFORD G. GRULEE, DR. HEYWORTH N. SANFORD, DR. PAUL HERRON, DR. JENNIE KANTOR-ANTMON and DR. HARRY SCHWARTZ.

Of 20,061 infants who were studied from birth to 9 months of age during 1924 to 1929, inclusive, 48.5 per cent were totally breast fed, 43 per cent partially breast-fed and 8.5 per cent artificially fed. The total morbidity of the breast-fed group was 37.4 per cent, that of the partially breast-fed group 53.8 per cent and that of the artificially fed group 63.6 per cent. The average mortality of these infants per year was 1.1 per cent. This mortality was 6.7 per cent in the breast-fed group, 27.4 per cent in the partially breast-fed group and 66.9 per cent among those artificially fed.

DISCUSSION

DR. H. E. IRISH: This is an excellent study and demonstrates effectively the superiority of breast feeding.

With respect to this situation, I have found that healthy women who have normal vitality and can nurse their babies are the type that bear babies that are more resistant to disease than those born of the type of women not able to nurse their babies. At the Cook County Hospital, particularly, babies born to women who are not able under any management to nurse their children are not as likely to be resistant to infection as the other type.

DR. MAXWELL P. BOROVSKY: Dr. Grulee has made a splendid plea for breast feeding, but I should like to inquire what he is able to accomplish in his private practice in regard to breast feeding. All pediatricians have difficulty in persuading many women to nurse their babies, and I should like to know how small an amount of breast milk he would consider necessary to make breast feeding worth while.

DR. S. C. HENN: I used to work with the Infant Welfare Stations and am in sympathy with the plea for breast feeding. These are impressive figures, but in regard to the type of mothers who came to the welfare stations, when they

could nurse the babies, there was not much to interfere with the type of food they received. When artificial feeding was used, many factors entered in. For example, many of them did not have ice, and often the milk was sour. In this connection, it is difficult to determine whether the better physical status of the breast-fed children was due to the breast feeding or to the type of artificial feeding that the other infants received.

DR. CLIFFORD G. GRULEE: There is something to be said for the position that Dr. Irish has taken, and it is the only valid objection, but with such a large number of babies the question of whether the mother had general debility would hardly stand. As to whether a woman who cannot nurse her baby has a congenitally debilitated baby or whether the child is generally debilitated as a result of not getting the proper nourishment, I think there is some question.

I can persuade a great many mothers to nurse their babies. As to the amount of milk that I think the mother should give the baby, that depends on how the baby acts when he gets the milk. Some infants do not show any disturbance, and I leave them on the breast. Some show disturbance when they get a few ounces, and I take those off.

As to the character of the food, I called attention to the fact that these figures were gathered at the height of national prosperity, from 1924 to 1929, and there was little difficulty then in getting proper food for a baby and having it properly taken care of. As to whether we selected the proper kind of food, we provided all the elements that are supposed to enter into an adequate food in the formulas. I doubt whether it is possible to feed such a large number of babies such formulas with better results. The death rate was one-fourth that for the other children in the district who were not cared for by the Infant Welfare Stations, so we were not so far wrong in the way in which we took care of the children.

SOME REFLEXES IN THE NEW-BORN. DR. CHARLES SCHOTT AND DR. THOMAS P. SALTIEL.

One hundred and seven new-born infants were studied during the first ten days of life. Of this number 2 proved later to be spastic paraplegic idiots. One had spina bifida with meningocele. In 2 marked differences in the neurologic findings compared with those in the other 102 led us to believe that they would eventually show some neuropathic signs.

The following points were considered in examination: (*a*) rigidity of the arms and legs, (*b*) abduction of the thighs, (*c*) flexibility of the back, (*d*) the patellar tendon reflex and (*e*) the plantar reflex.

The plantar reflex (Babinski's sign) was tested daily and showed a certain uniformity of reaction in 71 per cent of the cases. No deviation from the normal was noted in 2 cases of cerebral hemorrhage. This confirms more or less the observations of other investigators.

The patellar tendon reflex was almost uniformly present and showed no characteristic action in cases of intracranial lesions.

The degree of flexibility of the back and the degree of abduction of the thighs may frequently be considered as early signs of spastic tendencies.

DISCUSSION

DR. MAXWELL P. BOROVSKY: The work that my colleagues and I have been doing with tremors of the new-born at the Cook County Hospital has been primarily not with the reflexes but with the findings of irritability of the nervous system. We observe a tremor of the hands in a certain percentage of new-born babies, and sometimes the tremor involves also the lower extremities. Our original effort was to try to connect this condition in some way with cerebral hemorrhage. We believe that it is more likely due to cerebral concussion or cerebral edema, or, in many instances, is the result of toxemia on the part of the mother. The phase that we are now undertaking is in connection with the blood chemistry, and we

hope that we shall some day have an opportunity to report concerning the irritability of the nervous system as demonstrated by tremors in connection with the blood chemistry.

DR. THOMAS P. SALTIEL: The work on tremors was not considered in this particular study and was perhaps not known at the time we made the study.

BACILLUS PERTUSSIS HEMOPHILUS ENDO-ANTIGEN (KRUEGER). DR. G. F. MUNNS (inaugural thesis) and DR. C. A. ALDRICH.

During a recent epidemic of whooping cough in the village of Winnetka, Ill., and surrounding communities, Krueger's endo-antigen (Krueger, A. P.; Nichols, V. C., and Frawley, J. M.: Preparation of an Active Undenatured Antigen from Hemophilus Pertussis, Proc. Soc. Exper. Biol. & Med. **30**:1097, 1933) was used in the treatment of 122 patients in active cases and cases of exposure.

Fifty-five and five-tenths per cent of 45 children who received antigen because of known exposure did not contract pertussis. Among those who contracted pertussis, 75.2 per cent had moderate or mild attacks (57.7 per cent had mild attacks). Twenty-four and seven-tenths per cent had severe attacks. Eighty and three-tenths per cent of all the children who received the antigen either did not have the disease or had moderate or mild attacks. Sixty-six and four-tenths per cent either did not have the disease or had very mild attacks. The average duration of all the cases, including mild, moderate and severe cases, was 5.16 weeks. This is a relatively short period for a winter epidemic.

General reactions to the antigen did not occur. Local reactions were slight and of no consequence. There were no serious complications and no deaths.

Our experience indicates that the antigen probably is of most value when given before the onset of the cough or, if the cough has begun, within less than seven days following the onset. In some instances there was a favorable response when the antigen was given late in the attack.

This treatment probably will be of still greater value if the antigen is administered in larger and more frequent doses.

Our experience with the use of Krueger's pertussis hemophilus endo-antigen indicates that the majority of children who receive the antigen will have mild attacks of pertussis. Although the prophylactic effect is more uncertain, the antigen apparently has the definite effect of modifying and shortening the majority of pertussis infections.

DISCUSSION

DR. CLIFFORD G. GRULEE: I am much interested in the vaccine treatment of whooping cough. I have believed that it was never given its just due, because of an experience that I had twenty years ago. At that time I was on the staff of the Cook County Hospital and was the only pediatrician there. We had many patients with whooping cough; all contracted pneumonia. In sheer desperation we gave these patients whooping cough vaccine, and to my surprise 7 or 8 of them recovered. If one knows the type of pneumonia seen at the Cook County Hospital one can realize that this result was something of a surprise. As a consequence I have never lost my faith in whooping cough vaccine. I had one experience which caused me to think that if it is given early it will prevent whooping cough. I remember one family in which all the children had whooping cough except the youngest, who was 2 or 3 years old. That child received two or three injections of vaccine and did not contract whooping cough, although it was exposed to it all the time. I saw some of Dr. Sauer's work also, and I think that he has good proof of the value of this vaccine. One should not be too destructive in the consideration of whooping cough vaccine. I believe that there is some merit in it, but do not know how much.

DR. C. A. ALDRICH: I saw a great many of these cases, and I think that Dr. Munns was conservative in his grouping. I told him that all the cases in

the moderate group should have been called mild. An average duration of four weeks is an extremely short course for a winter epidemic of whooping cough. Dr. Munns has perhaps bent a little backward in his classification of cases. I have always used whooping cough vaccine and still do so, because after some fifteen or twenty years' experience I have found that bronchopneumonia has never developed in a patient treated with the vaccine, while many cases of bronchopneumonia have been seen in patients not so treated.

DR. ARTHUR F. ABT: I wish to compliment Dr. Munns on his paper. I should like to ask what the endo-antigen is, but take it that it is a vaccine comparable to the typhoid vaccine. I should like to know whether there is a negative phase, as in typhoid vaccine, before the immunity begins. If there is such a phase, I wonder how protective the antigen can be, if it is given just before an attack is expected.

DR. EDWIN P. RUSSELL (Berwyn, Ill.): About seven or eight years ago, when I was in Michigan, I published an article on 60 cases of pertussis and the use of vaccine. I was optimistic and enthusiastic and felt justified in my conclusions when I wrote the report. During the next epidemic I used the same vaccine and had no results. I have had the experience that vaccine works well in one epidemic and in the next is worthless. In none of the cases in which I used the vaccine was there any bronchopneumonia, as Dr. Aldrich said, but there were deaths from bronchopneumonia in other cases during the same epidemic when the vaccine was not used.

DR. G. F. MUNNS: There has not been enough work done with this preparation to answer Dr. Abt's question. Further work is being carried out in California.

DR. H. E. IRISH: Is this preparation a commercial product?

DR. G. F. MUNNS: It is. The antigen recently used is a more concentrated preparation, and results apparently are improved. I believe that the product is not on the market generally as yet.

CELIAC DISEASE (CHRONIC INTESTINAL INDIGESTION). DR. JULIUS H. HESS AND DR. O. SAPHIR.

Short clinical histories with detailed observations at autopsy on 3 young children are reported. While grossly the pancreas showed no noteworthy changes in any of the cases, histologically a severe fibrosis was encountered in 2 instances, with dilated ducts and seemingly large islands of Langerhans, some of which also revealed an increase of connective tissue. Scattered throughout was a slight lymphocytic infiltration. In the third case the changes as encountered in the hematoxylin-eosin preparations were much less severe, and only by the use of special staining methods (Van Gieson's method and Foote's stain for reticulum) a distinct new formation of connective tissue and reticulum was demonstrated. In the first 2 instances concrements were also found within the ducts.

It is extremely difficult to decide whether a difference exists between primary pancreatic disease in infancy and the clinical picture of celiac disease or whether they are identical. Burghard's, Gross' and Passini's cases, which revealed severe changes in the pancreas, are regarded as examples of celiac disease. The changes in the pancreas in Gross' case were almost identical with those seen in our first 2 cases. In our opinion, the most outstanding clinical symptoms of celiac disease, namely, the wastage of fat, can be explained on the basis of a primary pancreatic disorder. Because fibrosis was also present within the islands of Langerhans, we believe that it might also be possible to correlate the changes in the carbohydrate metabolism with pathologic changes in the pancreas.

Instances of celiac disease are described in the literature which revealed chronic diseases of the gastro-intestinal tract but no changes in the pancreas. If, by the use of special staining methods, it is not possible to demonstrate advanced fibrosis

in the pancreas, it must be conceded that the symptom complex of celiac disease has no definite pathologic entity. Our series, comprising only 3 cases, is too small to permit generalization. Because of our observations we must insist, however, that in every instance of celiac disease the pancreas should be studied with special methods before pronouncing it normal.

DISCUSSION

DR. I. M. LEVIN: Was examination of the stools carried out to determine the fatty acid and neutral fat content? The clinical diagnosis of celiac disease cannot be affirmed without definite fatty changes in the stool, some authors insisting that at least 20 per cent of fat must be obtainable. There are likewise changes in the normal relationship between gram-negative and gram-positive organisms and between bacilli and cocci. In true celiac disease depression in blood protein and cholesterol has been described. Were agglutination tests carried out on any of these patients to rule out the typhoid-dysentery-melitensis infections?

DR. H. E. IRISH: Has anything been reported in the literature to indicate whether the use of insulin-dextrose injected hypodermically has been tried in any of these cases?

DR. JULIUS H. HESS: There were no pathogenic bacteria in the stools; this refers to organisms of typhoid fever, parathyphoid infections and dysentery. In some of the cases reported in the literature the bacillus of dysentery was isolated. Our cases were all fatal, and in none was there enteritis of any degree. I think that none was examined directly for fatty acids, but in 2 the stools contained a great deal of neutral fat. Blood cholesterol studies were not made in any of them.

We did not use insulin in any of these cases. There have been some favorable reports from its use. We gave insulin over a short period to one patient, who is alive and well, but with the diet high in protein and low in carbohydrate we were fearful of going further. Following the pathologic demonstration here, I should say that this treatment would be well worth further trial. The question always arises of the long-continued use of insulin in this type of case, and I wonder whether one is justified in instituting insulin therapy in the average cases in patients who do well on a diet high in protein. Of course, it might give the pancreas a rest and assist in recovery and from this standpoint should be given serious consideration. However, careful, controlled clinical studies are necessary before insulin therapy is to be recommended for general use. Also, intestinal indigestion may be due to other causes than pathologic changes of the pancreas.

Annual Meeting, May 22, 1934

STANLEY GIBSON, M.D., *Vice President, in the Chair*

INTRACRANIAL TUMORS OF INFANCY AND CHILDHOOD. DR. PERCIVAL BAILEY (by invitation).

Intracranial tumors are of many varieties and cannot profitably be discussed as a whole. These tumors in infants and children are different pathologically from those in adults and have a different site. In children under 15 years of age 70 per cent of intracranial tumors are subtentorial. The most common pathologic types are astrocytoma, medulloblastoma and ependymoma. The most common supratentorial tumor in childhood is the craniopharyngioma.

The general signs of intracranial tumor (really of increased intracranial tension) in children do not differ from those in adults except in degree. Headache and swelling of the optic disks may be transitory because of separation of the cranial sutures. Vomiting, however, is almost constant and very precocious, because

of direct pressure on the vomiting mechanism in the bulb. The separation of the sutures causes enlargement of the head and a peculiar tympanitic sound on percussion of the head (Macewen's sign).

The ependymomas are typical of tumors in the fourth ventricle. There may be no symptoms except stiffness and abnormal position of the neck and pain radiating down the neck, but usually increased intracranial pressure and disturbance of equilibrium are also present. The tumors of the cerebellum proper have about an equal chance to be astrocytoma (a benign, usually cystic, easily removable tumor) or medulloblastoma; the latter is a malignant tumor, often infiltrating the leptomeninx over all the cerebral nervous system. The medulloblastoma is, moreover, markedly sensitive to radiation. In the posterior fossa occurs also a diffuse glioma of the brain stem, which is usually diagnosed as encephalitis. Whenever a child shows progressive palsies referable to the cranial nerves of the posterior fossa, glioma of the brain stem should be suspected, since inflammatory or degenerative diseases of this region of the brain are excessively rare in childhood.

In the supratentorial region the suprasellar tumors of the craniopharyngeal duct may be recognized in 85 per cent of cases from the telltale calcification visible above the sella turcica in the roentgenogram. They must be differentiated principally from the gliomas of the optic chiasm. The glioma dilates the optic foramina and is often associated with evidences of generalized neurofibromatosis.

Other rare tumors in the supratentorial region in children are pinealoma, papilloma of the choroid plexus, teratoma, sarcoma and angioma. The last type can sometimes be suspected from an accompanying facial nevus. Cerebral tumors of children often reach an enormous size before causing any localizing neurologic signs.

Tuberculoma is rare in the United States, except in the Negro population. Formerly, Starr reckoned 50 per cent of intracranial masses as tubercles. Even today in Leeds, England, statistics indicate that 66 per cent of intracranial masses in children are tubercles. The low incidence of tubercles in this country is eloquent testimony to our high standards of living. One hopes that President Roosevelt will be able to maintain it for our children.

The only treatment for these tumors is removal by surgical means, when possible; the medulloblastoma may be held in check by radiation.

DISCUSSION

DR. HENRY E. IRISH: Where was this material printed, if it has been published?

DR. PERCIVAL BAILEY: I have recently written a book on the subject, entitled "Intracranial Tumors." It was publishde by Charles C. Thomas of Springfield, Ill.

DR. VICTOR E. GONDA: May the fixed position of the head of the child indicate a connection between the growth and the circulation of the spinal fluid, the tumor acting as a sort of ball valve which in some positions, when the child moves the head, interferes with the movement of the spinal fluid?

DR. PERCIVAL BAILEY: I think that that is the explanation. The child holds the head in the position which it finds to be most comfortable by reason of allowing the fluid to circulate. If one forces the head out of that position, the sudden compression of the medullary centers may kill the child.

DR. JOHN A. BIGLER: I should like to ask about the percentage of tuberculomas in children, as they were not mentioned with the other tumors. How common are they, and how often do they present symptoms of tumor of the brain?

DR. PERCIVAL BAILEY: It was formerly stated that 50 per cent of the tumors in childhood were tubercles, but that is not true today. Within the five years that I have been in Chicago and have observed our material and that in the Children's Memorial Hospital I have seen only three tubercles. Tubercles nowadays

seem to be multiple and do not cause symptoms that lead one to think of tumors. The symptoms are usually those of encephalitis. Many of the children with so-called tubercles may have neoplasms. At any rate, one does not often see solitary tubercle of the cerebellum today.

DR. CRAIG BUTLER: I wish to ask about the prognosis in hemangioma of the meninges. Does this clear up under roentgenotherapy, and what is the prognosis if it is treated surgically?

DR. PERCIVAL BAILEY: It is dangerous to operate for hemangioma. It is difficult to tell in the tangle of blood vessels which is the entering one. Most attempts to deal with hemangioma surgically end in disaster. I know of one case in which roentgenotherapy did some good. The tangle of vessels which was disclosed on an attempted operation afterward became calcified, and it was possible to remove it. In another case, in which there was a bruit, this disappeared under roentgenotherapy. This treatment does not relieve the epilepsy that accompanies the condition, however.

DR. R. L. JENKINS: In estimating the enlargement of the head, how does one compare the measurements of the skull? There are such wide variations in these measurements between various racial types that I should like to know how adequate the available norms are.

DR. PERCIVAL BAILEY: I never pay attention to the absolute size of the child's head. The tympanitic sound that is heard when one taps on the head determines the diagnosis. After one hears this sound, one takes a roentgenogram, and in the roentgenogram one can see the separation of the sutures. The statement has been made by Dandy that the occipital protuberance is shifted upward in cases in which there is a tumor in the posterior fossa in children. Recently, I have been taking measurements in all my cases, and I doubt that such is a fact. Infants rarely have intracranial tumor. In the first year of life, when the head enlarges too rapidly one thinks of so-called idiopathic hydrocephalus if the enlargement occurs soon after birth, or of subdural hematoma if it occurs after the first six months of life.

DR. PHILIP L. ARIES: I wish to ask whether Dr. Bailey has found it possible to elicit the Macewen sign in tuberculous meningitis.

DR. PERCIVAL BAILEY: I have found it in only one case. Children with this disease usually die before their sutures are much separated.

DR. ABRAHAM LEVINSON: I should like to ask Dr. Bailey's opinion regarding the danger of spinal puncture in tumors of the brain in children and also whether he has any information about changes in the cerebrospinal fluid in tumor of the brain.

DR. PERCIVAL BAILEY: Lumbar puncture is often unnecessary, but whenever I think that it is necessary I do it. If the intracranial tension is extremely high, I prefer to make a hole in the skull and puncture the ventricle. I feel more comfortable in doing this than in making a lumbar puncture. I have never had a patient on my service die as a result of making a lumbar puncture, but in the hospital during the last two years two deaths occurred following this procedure. If a lumbar puncture is made in such cases, it must be made in a situation where rapid action can be taken. There are plenty of records of death from this measure in the medical literature.

As to the changes that occur in the spinal fluid in tumor of the brain, ordinarily there are none. However, if the tumor impinges on the subarachnoid space or the ventricles, one may observe xanthochromic fluid and an increased number of cells. Whenever I suspect tumor and see an increased number of cells, I precipitate these cells and stain them, and often find that they are not lymphocytes but tumor cells. In some cases of intracranial tumor there may be a weakly positive Wassermann reaction, even though no syphilitic infection is present.

DR. ABRAHAM LEVINSON: In view of what has been said, is there any rationale for encephalography in tumor of the brain?

DR. PERCIVAL BAILEY: I prefer not to do it. Often the air will not go into the ventricular system. I prefer to make a direct injection of air into the ventricles. I think also that it is easier to interpret a ventriculogram than an encephalogram. It is difficult to interpret the shadows in either one but I find it easier to do this in the ventriculogram. In the third place, there is some danger in taking encephalograms in cases of increased tension. The patients often suffer more as a result of this procedure. In the fourth place, if one punctures the ventricle, one has a hole through which one can let fluid out, and the patient is relieved. However, if the patient does not have any symptoms of increased intracranial pressure and I make a spinal puncture and find no increased pressure, I take encephalograms in some cases, even though I suspect a tumor.

DR. M. L. BLATT: I have believed that intracranial abscesses are more common in children than tumors and should like to know what Dr. Bailey's experience is in this regard and how he differentiates between these two conditions.

DR. PERCIVAL BAILEY: One must often consider that there has been a suppurating ear or a suppurating sinus and that at some time during this suppuration there have been symptoms indicating infection in the form of some fever which does not seem to be accounted for by the amount of infection in the ear or sinus. If there is such a history, one would be led to suppose that there is abscess rather than tumor. In cases in which there is no increased tension, I do not hesitate to make a lumbar puncture; in this way one may find something in the fluid which will help. Again, the pulse rate may be slow, and this is rare in tumor. If one finds an extremely slow pulse rate with a subnormal temperature and no increase in intracranial tension, and if there is a history of suppuration about the head, one may suspect an abscess, but in many instances no one can be positive as to whether the condition is an abscess or a tumor. Of course, one is constantly encountering children who have had infection of the middle ear and who afterward have a tumor. There is always that differentiation to make. I have taken out an abscess which I had diagnosed as a tumor and which I did not know was an abscess until it was cut in the laboratory. Other surgeons have done the same. Differentiation is not always possible.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS AND SECTION OF SURGERY

Combined Meeting, April 12, 1934

MARTHA WOLLSTEIN, M.D., *Presiding*

TWO CASES OF PNEUMOCOCCIC PERITONITIS. DR. JOHN V. BOHRER.

CASE 1.—S. P. was admitted to the children's surgical service of Bellevue Hospital on Feb. 25, 1924, at 6 years of age. Two days before admission she had fever and complained of sore throat. She was put to bed and given a laxative. The bowels moved the following day. They remained loose, and the condition amounted to diarrhea for several days thereafter. She had eaten little food, but had drunk much water.

On the second day of her illness she became nauseated and vomited. On admission to the hospital she complained of slight pain in the abdomen, fever, sore throat and frequent bowel movements. Her past history was entirely unimportant. She had been subject to neither sore throat nor abdominal pain.

On physical examination she appeared well developed and well nourished. Although it was evident that she was very ill, she did not appear to be in great pain. Respirations were fast and shallow. There was marked circumoral pallor. The skin was dry and hot; the eyes were sunken, and she was evidently much

dehydrated. The tongue was coated and dry, and the tonsils were enlarged and red, but no exudate was observed. The chest was normal. Fluoroscopic examination gave negative results. The abdomen was distended, tympanitic and tender, with generalized rigidity, which varied in intensity. No masses could be felt. There was distinct pain on abdominal pressure, but it could not be localized to any quadrant; it was, however, more severe in the lower part of the abdomen. Rectal examination was not helpful in making a diagnosis. The temperature was 103.2 F., the pulse rate 150 and the respiratory rate 30.

The urine contained albumin (a trace), but no pus cells and no casts. A blood count showed 25,000 white cells, with 93 per cent polymorphonuclear cells.

The abdomen was opened through a lower right rectus incision. Five hundred cubic centimeters of free fluid was encountered as soon as the peritoneum was opened. This was brownish and odorless and contained flakes of fibrin rather than pus. There was a diffuse, purulent, plastic exudate involving the entire peritoneum, the parietal as well as the visceral portion. The coils of the intestines were loosely glued together with this plastic exudate. The appendix was not noteworthy, except for considerable plastic exudate at its base. It was obviously not the seat of an infection causing the peritonitis, but was removed. A culture was taken, which was later reported to show pneumococci. Two rubber dam drains were placed in the pelvis, and the peritoneum was closed with interrupted chromic catgut, the drain being allowed to emerge at the lower angle of the wound. The incisions in the muscles, fascia and skin were not closed.

Just before the operation the patient was given a hypodermoclysis of 500 cc. of a physiologic solution of sodium chloride containing 5 per cent dextrose. This was repeated daily for the ensuing week. The postoperative temperature ranged from 101 to 104 F. during the first week and from 99 to 101 F. during the second week and became normal during the third week. The patient was given 50 cc. of pneumococcic antibody subcutaneously daily for the first three postoperative days. Her wound drained profusely for ten days. The drains were removed on the seventh postoperative day, and the wound healed until there was only a sinus. The patient was out of bed at the end of three weeks and was discharged from the hospital within thirty-seven days. She returned to the outpatients' clinic because of the sinus, which continued to discharge a small amount of pus for the following three months, after which it closed and has remained closed. At present the patient is normal and healthy.

CASE 2.—M. S., 8 years of age, was admitted to the Willard Parker Hospital on Nov. 10, 1925. She had been in another hospital on account of sore throat, vomiting, fever and pain in the lower part of the abdomen on the left. After five days she was transferred to Willard Parker Hospital because of a fine punctate rash which was believed to be scarlet fever. She was given an initial dose of scarlet fever serum, but it was soon evident that the rash was of a toxic type.

Physical examination showed a well developed and well nourished child who was acutely ill. The face was flushed, the eyes sunken, the lips dry and cracked and the tongue strawberry in type. The pharynx was inflamed, and the tonsils were hypertrophied, with an exudate on the right tonsil. The breath was malodorous. A diagnosis of pneumonia of the lower lobe of the right lung was made on the basis of physical signs and confirmed by roentgen examination. The circulatory system was normal except for an increased heart and pulse rate and slight cyanosis. Generalized tenderness of the abdomen with marked distention was noted, but there were no masses or localized tenderness. A generalized punctate erythematous rash involved the entire skin. Neurologic examination gave negative results.

Urinalysis showed nothing abnormal except marked concentration of urine, albumin (a trace) and an excess of indican. The leukocyte count ranged from 22,000, with 94 per cent polymorphonuclears, on admission to 18,000, with 84 per cent polymorphonuclears, on Jan. 3, 1926. A blood culture was reported positive for pneumococci. A vaginal smear for pneumococci was negative.

On admission the temperature was 103 F. and ranged between 101 and 104 F. for the ensuing five weeks, after which it gradually subsided, with frequent sharp elevations, to normal. The pneumonia promptly subsided, but the temperature remained of the septic type, and repeated blood cultures demonstrated pneumococci. The tenderness and distention of the abdomen persisted, and eighteen days after admission a surgical consultant suggested the possibility of pneumococcic peritonitis. Thirty-eight days after admission, owing to the presence of a fluid wave and shifting dulness, paracentesis abdominalis was performed, and a huge quantity of pus was withdrawn. The infecting organism was proved by culture to be a pneumococcus.

Under local anesthesia a small incision was made below the umbilicus, and a tube was inserted into the localized intraperitoneal abscess. Multiple superficial abscesses later developed, the most severe of which was in the region of the left hip joint. It was extensive but did not invade the joint. These abscesses were incised after they became fluctuant and well localized. On January 19, the patient was transferred to the children's surgical service at Bellevue Hospital, where she completed her slow convalescence. She was discharged on April 1, with all the wounds healed and the abdominal sinus closed. She has remained well and is now entirely normal.

NEPHROSIS COMPLICATED BY PNEUMOCOCCIC PERITONITIS. DR. PHILIP D. ALLEN.

M. S., a girl, aged 2 years and 10 months, was admitted to the pediatric service of Bellevue Hospital on Nov. 24, 1933, and transferred to the children's surgical service on Jan. 6, 1934.

The family history was unimportant. The patient had been born by a normal spontaneous delivery. She had whooping cough at 2 years of age and had an occasional cold.

Three and a half months before admission she had a painless swelling of the legs, abdomen and face. Treatment was instituted at home, and the edema subsided within six weeks. She remained well for five weeks; then the edema returned following a cold and persisted up to admission. The urinary output had been gradually diminishing for the past three weeks, and on the day before admission the output was 4 ounces (118 cc.), with an intake of 29 ounces (855.5 cc.) of fluid. There had been a mild cough for the past week.

Physical examination showed a girl weighing 36 pounds (16.3 Kg.), with a waxy color and marked edema of the face, abdomen and legs. The blood pressure was 108 systolic and 75 diastolic. The temperature was 99 F., the pulse rate was 100, and the respiratory rate varied from 20 to 26. The lungs revealed dulness and diminished breath sounds at both bases. There were no râles, and the upper two thirds of the lungs were normal. The abdomen revealed an almost obliterated umbilicus with a definite fluid wave and shifting dulness. The urine was acid, with a specific gravity of 1.040, albumin (four plus), and a few hyaline casts. The white blood count was 15,400 with 60 per cent polymorphonuclears.

On November 27, the condition remained unchanged. Chemical examination of the blood revealed nonprotein nitrogen, 50 mg. per hundred cubic centimeters; chlorides, 450 mg.; cholesterol, 500 mg.; protein, 3.65 Gm.; albumin, 1.08 Gm.; globulin, 2.57 Gm.; calcium, 8.7 mg., and phosphates, 4.5 mg. The patient was given ¼ grain (0.016 Gm.) of thyroid extract three times daily. The intake of fluid was still far in excess of the output.

On December 3, the temperature rose to 101.8 F. The edema was less. The patient complained of abdominal pain and was irritable. She vomited occasionally and had mild diarrhea. The urinary output increased. The abdomen revealed increasing distention and much fluid. There was diffuse tenderness, but no local tenderness, and no masses were present. Urinalysis revealed a specific gravity of

1.050, with less albumin and more hyaline casts than on previous examinations. A blood count revealed 6,000,000 red blood cells and 24,400 white blood cells, with 61 per cent polymorphonuclears.

On December 5, the temperature remained at about 101 F. Cellulitis of the lower part of the abdominal wall appeared, which extended up to the umbilicus. This was red, but the margins were not raised. The abdomen was still distended and tender. The patient was seen by Dr. Beekman, the surgical consultant, who diagnosed the condition as pneumococcic peritonitis, but who favored observation until localization should occur.

On December 13, the temperature remained slightly elevated. The patient had lost 9 pounds (4.1 Kg.) within one week. Cellulitis disappeared from the abdomen and appeared over the lower lumbar region.

On December 19, chemical examination of the blood revealed nonprotein nitrogen, 25 mg. per hundred cubic centimeters; cholesterol, 158 mg.; chlorides, 500 mg.; protein, 6.03 Gm.; albumin, 2.81 Gm.; globulin, 3.22 Gm.; calcium, 6.9 mg., and phosphates 5.5 mg. A blood culture was sterile.

On December 29, the fever continued. The right ear drum ruptured spontaneously, discharging a serosanguineous fluid. The urine revealed only a faint trace of albumin. The swelling on the back was fluctuant.

On Jan. 1, 1934, an incision was made on either side of the midline in the lumbar region, and about 30 cc. of light green pus was obtained from two separate pockets. Culture of the pus revealed pneumococci of an unclassified type.

On January 5, the temperature was about 101 F. The umbilicus revealed a pointing abscess, and a mass occupying the lower midportion of the abdomen could be felt. On rectal examination the mass could be felt toward the anterior midline; it did not extend into the pelvis.

On January 9, an elliptical incision was made just below the umbilicus, extending through the peritoneum. Several ounces of pus was obtained. On exploration with the finger, a cavity was found, extending down to the pubis. No intestines were encountered. The cavity was drained. Three days later a fluctuant area on the left thigh was drained. Cultures from the wound revealed Pneumococcus type XXIX.

On February 6, all the wounds were still draining. The temperature was about normal.

On February 22, chickenpox developed, and the child was sent to the Willard Parker Hospital, where she remained until March 5, when she returned to Bellevue Hospital. There was still slight draining from the abdominal wound. Urinalysis revealed a specific gravity of 1.019, with no albumin. The patient was discharged on March 14, with the wounds closed, in good general condition. She has remained well and has gained weight since discharge.

This case is presented as a typical case of pneumococcic peritonitis complicating nephrosis. I believe that the successful outcome was due to the withholding of any surgical procedure until the abscesses were well localized.

PNEUMOCOCCIC PERITONITIS FROM THE PEDIATRIC POINT OF VIEW. DR. MURRAY H. BASS.

The literature on pneumococcic peritonitis in childhood is reviewed. Nineteen cases of this disease seen in the pediatric and surgical services of Mount Sinai Hospital during the past twelve years are analyzed.

The use of peritoneal puncture in making a rapid diagnosis is advocated. From a consideration of the cases seen by me and my colleagues and from the most recent reports in the literature, it seems best to postpone the operation until the initial shock of the onset is over and the peritoneal process has been localized. The mortality in the series studied is the same as that found in several hundred previously reported cases, namely 58 per cent.

SURGICAL ASPECTS OF PRIMARY PNEUMOCOCCIC PERITONITIS. DR. EDWARD J. DONOVAN.

Primary pneumococcic peritonitis is one of the most serious of the acute abdominal conditions with which the surgeon has to deal and probably has the highest mortality. Fortunately, it is infrequent; I found only twelve cases recorded at the Babies' Hospital and St. Luke's Hospital within the past ten years. During the same period there have been two hundred and thirty-three cases of general peritonitis due to ruptured appendixes and twenty-five cases due to Streptococcus in these hospitals.

Pneumococcic peritonitis may be primary or secondary, localized or diffuse. In the primary variety, which is the type under discussion tonight, it is understood that the peritonitis is the primary manifestation of the disease.

The surgeon is interested in the manner in which the infection reaches the peritoneum, but his chief concern is in the pathologic changes, the diagnosis, the treatment and the high mortality. The pathologic changes found at operation are fairly characteristic and often are the first intimation that the surgeon has that he is dealing with primary peritonitis. The exudate is profuse, odorless and green or greenish brown and contains many flakes of fibrin. In the early cases

Data for Twelve Patients with Primary Pneumococcic Peritonitis

Age at Incidence		Leukocytes		Time of Death after Operation	
2	under 1 yr.	2	10,000	1	12 hrs.
1	under 1¼ yrs.	1	16,000	1	24 hrs.
4	between 5 and 6 yrs.	1	20,000	2	48 hrs.
2	aged 8 yrs.	1	21,000	1	4 days
1	aged 27 yrs.	2	22,000	1	6 days
1	aged 38 yrs.	1	34,000	1	8 days
1	aged 42 yrs.	1	42,000	2	17 days
		1	52,000		
		2	Not reported		

it is confined to the pelvis, and acute salpingitis may be evident, as in one of the cases in the series studied. The peritoneum is red, edematous and thickened, and there is a definite tendency for the coils of the intestine to adhere to one another with large plaques of fibrin. Other cases may show a well localized infection which tends to form an abscess at or near the umbilicus.

In many cases of primary peritonitis the condition is thought before operation to be due to a ruptured appendix. The clinical picture in primary peritonitis may be different from the picture in peritonitis due to a ruptured appendix. In primary peritonitis the child is apt to look much more ill and more toxic, and show much more prostration. The temperature is usually higher, and the condition may be ushered in by a chill. The abdomen has a doughy feel and shows less muscular rigidity and more diffuse tenderness than in the usual cases of ruptured appendix. Fortunately, most physicians have in mind the fact that acute appendicitis may resemble any of a number of different abdominal conditions, that any of the clinical features which are considered typical of acute appendicitis may be absent in any particular case, and that inflammation of the appendix is by far the most common cause of these symptoms in children. The error in diagnosis therefore seems justifiable and will probably continue to exist unless one does an abdominal puncture as a routine, as has been recommended by Dr. Newhof.

Transfusion of whole blood after operation is helpful and should be done as often as is indicated. In cases in which the organism is Pneumococcus type I the patients should receive serum. Aside from these procedures, the usual supportive measures for maintaining the fluid balance should be used.

There are several factors which contribute to the high mortality. Children with this condition are very ill from the outset and are, therefore, poor surgical risks, no matter how short a time the operation takes. Every surgeon recognizes the fact that it is mechanically impossible to drain the peritoneal cavity thoroughly. Fortunately, the peritoneum has the power of combating infection to an extraordinary degree. It is this power to combat infection, plus the drainage, that enables any patient with diffuse peritonitis to get well. One cannot help but think that the peritoneum may not have the power to combat the pneumococcus as vigorously as it does the colon bacillus.

McCartney and Frazier believe that all cases of pneumococcic peritonitis found in males are secondary to a focus of pneumococcic infection elsewhere, and that primary pneumococcic peritonitis is found only in young girls, in whom the infection reaches the peritoneum through the genital tract. I agree with these authors and have reached this conclusion through a study of the cases reported tonight and a detailed study of the autopsy reports on twenty-eight cases of pneumococcic peritonitis in the Babies' Hospital.

The table gives statistics for twelve cases of primary pneumococcic peritonitis seen in St. Luke's Hospital and the Babies' Hospital during the past ten years. All the patients were treated surgically, and three recovered. In three of the twelve cases the organism was Pneumococcus type I, and in five, Pneumococcus type IV; in the remaining four the pneumococcus was not typed. Two of the patients of the first group received serum; one recovered.

PNEUMOCOCCIC PERITONITIS IN NEPHROSIS. DR. JOHN D. LYTTLE.

I have been interested chiefly in the prognosis and treatment of nephrosis in children. Since the chances for the ultimate cure of nephrosis are fairly good, if pneumococcic infection can be avoided, the importance of diagnosis and treatment of pneumococcic peritonitis is apparent.

The figures in the literature show a mortality of from 40 to 60 per cent, due chiefly to pneumococcic peritonitis and bacteremia. There have been seventeen cases of nephrosis, or the "nephrotic syndrome," at the Babies' Hospital. There were nine deaths—a mortality of 53 per cent. In eight cases the cause of death was known, and in five it was proved to be pneumococcic bacteremia with peritonitis.

I have had the opportunity of studying Dr. Tappan's analysis of the material at the Harriet Lane Home in Baltimore. Her study is based on forty-five cases followed for from one and one-half to ten and one-half years. There were twenty-three deaths—a mortality of 51 per cent. She found that two factors modified the prognosis in nephrosis: first, the presence of true hematuria and, second, the development of pneumococcic peritonitis. If neither of these factors was present, the child had an 81 per cent chance of living and a 38 per cent chance of full recovery. If pneumococcic peritonitis alone was added to the picture, the chance of living dropped to 58 per cent and that of full recovery to 24 per cent.

Tappan noted that twelve of the forty-five patients showed hematuria or had glomerulonephritic episodes. Of these, nine died, but only two died as a result of pneumococcic infection (one of pneumonia and one of pneumococcic peritonitis), while six died of renal insufficiency. In my series three patients had glomerulitis superimposed on nephrosis. While infection was present at the time of death in all three, it was pneumococcic in only one, and in all three cases uremia was a more important factor as a cause of death than was the infection. In five of the six cases of pure nephrosis death was directly due to pneumococcic peritonitis; in these cases there was no evidence of renal failure. Why the patients with mixed cases should have escaped pneumococcic infection is an interesting and unexplained fact.

There seems to be no satisfactory treatment for pneumococcic peritonitis, so it would seem profitable to pay some attention to prophylaxis. In my experience, peritonitis usually develops in the active, edematous stage of the disease, and

infection of the upper or lower respiratory tract is always present. The presence or absence of erysipeloid has not seemed to be significant. The difficulties in getting rid of edema, raising the serum protein level, maintaining nutrition and avoiding contact with infections are too well known to need discussion. Yet these are the important things to do in order to prevent infection. Dr. Dawson asked whether any attempts had been made to immunize these children. That seems a good suggestion, and in view of the fact that there is an enormous amount of work being done on pneumococcic infection, physicians might make more energetic efforts to immunize these patients by means of vaccination or other methods of immunization against pneumococcic infection.

DISCUSSION OF THE PAPERS ON PRIMARY PNEUMOCOCCIC PERITONITIS

DR. HAROLD NEUHOF: The readers of the papers have fully shown that there are no surgical aspects, so far as operation is concerned. They have pointed out that the best chances for survival exist if operation is not performed until a localized abscess develops. Simple drainage can then be instituted. The crux of the problem is the diagnosis. That this can often be made on purely clinical evidence has been well shown this evening. In many cases, however, the diagnosis remains doubtful. It is for these cases that I advocate abdominal puncture. About eight years ago Dr. Ira Cohen and I reported the use and the technic of abdominal puncture in the diagnosis of acute intraperitoneal infections. Since that time we have employed the method in additional hundreds of cases. We have made no change in the technic other than to eliminate the small cutaneous incision. We employ a lumbar puncture needle now, as we did then. The needle is not to be deeply introduced, because fluid is always to be found just within the peritoneum, floating on the intra-abdominal viscera. There have been no untoward results in the large amount of material which we have had. At the time when our paper was read we were in doubt as to the significance of negative results of puncture. We know now that even the smallest amounts of fluid can be picked up. Negative results of puncture indicate, therefore, an absence of intraperitoneal fluid. It is safe to say that the diagnosis of pneumococcic peritonitis can always be made by abdominal puncture. I know of only one case in an adult in which pneumococcic peritonitis was derived from acute appendicitis. In a child the demonstration of pneumococci in intraperitoneal exudate eliminates the appendix as a possible source of the infection.

At a meeting of the surgical section of the Academy about a year ago, abdominal puncture was discussed and its dangers were emphasized. I am unaware of them and believe that abdominal puncture is a safer procedure than thoracic puncture. There is no more reason for a physician to employ thoracic puncture than abdominal puncture. If surgeons are averse to abdominal puncture, perhaps internists will employ the method and lead the way, as they did in the case of thoracic puncture.

DR. WILLIAM HEEKS: From the papers read this evening it is apparent that the diagnosis of primary pneumococcic peritonitis is not always made early and that the treatment is not standardized.

Vaginal smear is an important diagnostic aid and should always be made. Peritoneal puncture, although a disputed procedure, has many advocates who insist that it does no harm, and I believe it to be helpful, although I should like to cite briefly a recent case exemplifying the confusion which may occur in the bacteriologic examination of the peritoneal exudate:

A 4 month old boy was admitted to the Babies' Hospital with a history of abdominal pain and distention of a week's duration. He had been seen at the onset of his illness by the family physician, who thought that the child might have appendicitis. A consultant advised that there was no acute abdominal condition, and the child was kept at home, the abdominal symptoms meantime increasing. Acute otitis was also present. The child was finally brought to the hospital, and

the findings left no doubt as to the presence of an acute intra-abdominal inflammatory lesion. Because of the sex and the fact that the first impression of the family doctor was that the condition was appendicitis, laparotomy was performed. Diffuse peritonitis of a primary nature was found. The child died on the tenth postoperative day.

A smear of the peritoneal exudate showed organisms resembling Streptococcus, and a culture was reported as showing Streptococcus haemolyticus, but after forty-eight hours a final report of Pneumococcus was given.

The point of this case is, first, that a definite diagnosis of the infecting organism is not always possible at an early period and, second, that if Streptococcus is suspected, particularly in a male child, laparotomy should be strongly considered, because in any series of cases of acute appendicitis with peritonitis a definite number are found to be due to Streptococcus. To overlook acute appendicitis is a serious error, and in doubtful cases early operation is probably the wisest procedure.

In these papers little attention has been given to the complications, but it is sufficient to say that suppurative pleurisy is the commonest. Distention is frequently a distressing symptom, and in my experience is best controlled by the use of a Levin tube, inserted intranasally and left in place constantly, excessive loss of fluid being controlled by periodic clamping of the tube.

In conclusion, I would stress three important factors in treatment: first, the continuous administration of adequate amounts of fluid by the intravenous method; second, frequent small transfusions and, third, the use of specific antipneumococcic serum in suitable cases.

Book Reviews

Practical Pedodontia, or Juvenile Operative Dentistry and Public Health Dentistry. By Floyde E. Hogeboom. Third edition. Price, $6.50. Pp. 328, with 259 illustrations. St. Louis: C. V. Mosby Company, 1933.

The volume is the third edition, in the preface of which the author mentions having completely rewritten the text. He has added the following chapters: Mental Hygiene Viewpoints of the Child, by Forrest N. Anderson, M.D., Sc.D., Los Angeles; Prophylactic Odontotomy, by Thaddeus P. Hyatt, D.D.S., F.A.C.D., New York; Prevention of Dental Caries by Nutrition, by Harold F. Hawkins, D.D.S., Los Angeles, and Anesthesia for Children by Harry E. Straub, D.D.S., Los Angeles.

The work is in the nature of a textbook of children's dentistry, in which exposition of technical procedures is accompanied by chapters dealing with the theory and practice associated with this phase of dentistry. The material contained in Dr. Hawkins' chapter "Prevention of Dental Caries by Nutrition" is of particular interest, not only because of the data presented in substantiation of his belief that the cause of dental caries and pyorrhea alveolaris is a faulty "acid base balance" and "calcium phosphorus balance" but also because it outlines the author's treatment of the dietary aspects of these nutritional disturbances in a manner applicable to private clinical practice. The explanations for the findings in this chapter still await confirmation of more general research studies before they assume a crystallized character generally considered appropriate for textbook material.

In the chapter "Endocrinology and Its Relation to Dentistry" Dr. Hogeboom has summarized much of the present data in this field and has recognized the immaturity of the present state of knowledge. There is, perhaps, a tendency to emphasize hereditary and endocrine factors in the production of malocclusion at the expense of the functional mechanism through which these malformations become manifest. The emphasis on prophylactic treatment of structural defects, as presented by Dr. Hyatt, representing studies on 12,753 persons, is convincing evidence of the importance of a procedure extremely valuable in prophylactic treatment of dental caries in children.

The rules of Dr. Laurence W. Baker for the extraction of the first permanent molars, which Dr. Hogeboom presents in chapter 10, are open to question, as there is, both in the literature and in the minds of clinicians, some question of the frequency with which second permanent molars replace, without tipping, the first molars lost by extraction.

The section "Public Health and Dentistry" supplies a brief résumé of several of the outstanding developments in this field within the past few years and represents an advancing trend of thought in this important direction.

Brucella Infections in Animals and Man. By I. Forest Huddleson. Price, $2.25. Pp. 82, with 24 illustrations and 7 tables. New York: The Commonwealth Fund, 1934.

In the preface the author states that he "has endeavored to bring together as clearly and concisely as possible satisfactory methods and fundamental information which will aid the laboratory worker in the diagnosis and study of Brucella diseases, and the clinician in the interpretation of the results derived from the use of the methods in the laboratory." In this well written book he has succeeded in accomplishing his purpose. There is a short history of the three species of Brucella and a discussion of their classification, morphology and staining and cultural characteristics. The chapter on methods of isolating Brucella concisely

and clearly outlines the preparation of mediums for the growth of the organism and then gives directions for the obtaining of material from cattle and other animals which are infected by Brucella and also from human beings. There is a short but clear description, with plates, of the pathologic changes in Brucella infection in animals and man.

The next three chapters deal with the various methods of making a diagnosis of Brucella infections in animals and in man. The serologic methods are discussed, with directions for the preparation of the material used in these tests, and the technic of making the tests is clearly described. The allergic methods of diagnosis are discussed, and the preparation of material, technic and interpretation are clearly described. The method of determining Brucella infections by measuring the opsonocytophagic power of the blood is also given, with a clear discussion of the interpretation of the test. A detailed description of methods of differentiating the three species makes up the last chapter. There is an excellent bibliography, which in itself makes this book of real value. Although this book would be, perhaps, of special interest to the bacteriologist or the technician it is also of practical value to the practicing physician.

Chronic Nephritis and Lead Poisoning. By L. J. Jarvis Nye, M.G., Ch.M., Brisbane, Australia. Cloth. Price, 12 shillings, sixpence. Pp. 138. Sydney: Angus & Robertson, Ltd., 1933.

In this interesting monograph the author discusses the extreme frequency of chronic nephritis in the children and adults of Queensland, largely from the standpoint of etiology. He shows from statistical and clinical data that the disease is not due to infectious agents in this locality. On the other hand, he found that from 35 to 48 per cent of the victims gave previous histories of having had clinical lead poisoning, a condition extremely prevalent in this part of the world. It is considered that this comes about because of the action of the sun and extreme heat on the lead paint used on houses and fences, causing it to blister, peel and powder. Children handling these dried surfaces transfer the lead from hands to mouth by thum-sucking and nail-biting. The author states: "First, in the nephritis of young adults lead is the first aetiologic factor to be excluded; secondly, every child suffering from lead poisoning is a potential chronic nephritic." He believes that the lead exerts sclerosing effects on the general arterial system rather than on the kidneys alone.

While this work has its greatest value locally in calling to attention the need for public health regulations as to the use of lead paints, it also is of great interest to those who believe that chronic nephritis is not always due to infection elsewhere in the body. If there are in Queensland hundreds of patients with lead nephritis, there must be many similar cases elsewhere. As the author did not mention the occurrence of early edema in his nephritic patients, the type cannot be that most commonly seen in this country.

Children, Young People and Unemployment. Part III. Price, $0.50. Pp. 107. Geneva, Switzerland: The Save the Children International Union, 1934.

In the third and last part of the series of pamphlets published by the Save the Children International Union on the Effects of Unemployment on Children and Young People one finds reports on the situation in Bulgaria, Esthonia, Finland, France, Hungary, Norway and Sweden. Paul Wets, judge of the Children's Court at Brussels, sums up the opinions—on the whole, negative—of his colleagues in Belgium with regard to the influence of unemployment on juvenile delinquency; and F. Sempkins, secretary of the International Bureau for the Suppression of Traffic in Women and Children, comes to a similar negative conclusion with regard to prostitution among the young, although a general laxness in sexual morality has to be admitted.

The general conclusions drawn from the whole inquiry make it clear that the influence of unemployment on the physical health of the child is scarcely to be separated from the grave effects of the general distress caused by the economic crisis. On the other hand, the child of parents who are out of work suffers psychologically much more than does the child of parents whose poverty is due to other causes, particularly on account of the atmosphere of insecurity and tension prevailing in the home, not to speak of the changed relations between the different members of the family. The psychologic effects are much more striking in the case of the unemployed young person, for whom, while waiting for an easing of the labor market, work of some sort is the only really efficacious relief measure.

Lessons on the Surgical Diseases of Childhood. By William Rankin, M.B., Ch.B. Price, 21 shillings. Pp. 190, with 279 illustrations. Glasgow: Alex MacDougall, 1934.

This is a valuable addition to the well recognized works on surgery pertaining to infancy and childhood. It is a book of one hundred and ninety pages, made up of notes, lectures and descriptions of demonstrations given to students in their final year at medical college, and is designed to represent merely the ground work or introduction to this interesting field. This objective has been accomplished in a masterful fashion, and no one could read this little book word for word, as the reviewer has, without gaining the impression that the author is a surgeon of wide experience and good clinical judgment, possessed with the rare faculty of stating his views briefly and clearly. This book is above all things practical, as it is unusually well illustrated with photographs, roentgenograms and pen sketches, giving the reader the benefit of the author's opinions on the most important points in the diagnosis, clinical course and methods of treatment of surgical conditions with which the average student is most likely to come in contact during his internship and early years of practice. There are some ideas expressed with which most American surgeons would not whole-heartedly agree, but behind every statement there is undoubtedly a background of ample clinical experience. No medical student or practitioner of surgery would make a mistake in having this little volume as a part of his medical library.

Traité de médecine des enfants. Volume III. By P. Nobécourt and L. Babonneix. Price, 150 francs. Pp. 1,088, with 287 illustrations. Paris: Masson & Cie, 1934.

This is the third volume of the French system two volumes of which have already been reviewed.

In general, this volume carries on much the same as the others. It takes up the circulatory, respiratory and gastro-intestinal systems. The chapter on bronchopneumonia is especially good. The illustrations in some places are not as good as in previous volumes, but those on the mediastinal shadows are especially clear. The defect of this volume is that of the previous ones, that is, there is almost a total lack of reference to foreign literature, although in many of the conditions described outstanding work has been done by investigators who are not French. The gastro-intestinal disturbances are extensively treated. On the whole, the book is creditable.

Traité de médecine des enfants. Volume IV. By P. Nobécourt and L. Babonneix. Price, unbound, 150 francs; bound, 170 francs. Pp. 960, with 372 illustrations and 2 colored plates. Paris: Masson & Cie., 1934.

This fourth volume of the French system of pediatrics completes the discussion on diseases of the intestinal tract and takes up diseases of the genitourinary tract, intoxications, diseases of the bones and of the skin and eyes and psychiatry. As in the treatment of subjects in the other volumes, this work is detailed and well illustrated. Again the work of Péhu on syphilis

of the bone stands out; the illustrations are beautiful and well chosen. The portion on the diseases of the skin by Sézary and his collaborators is beautifully done and is illustrated with excellent photographs. One colored plate in this section is well chosen and gives an excellent picture of infantile eczema. The illustrations in the chapter on mental deficiency by Heuyer are exceptionally good, as would be expected from an author whose attainments in this field are so great.

Radiodiagnostico en la infancia. By Manuel y Francisco Arce. Pp. 285, with 90 plates. Madrid: Ediciónes Boro, 1933.

This is the first volume of a contemplated series on the roentgenology of infants and deals with the pelvis and extremities. The normal findings are well illustrated and discussed, and conditions such as osteitis, coxalgia, periostitis, tuberculosis, coxa vara and valga, osteochondritis, syphilis, scurvy, osteitis fibrosa, congenital deformities, fractures and luxations are taken up in detail. The plates are well chosen, and the descriptions of the various conditions are complete.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Professor G. Scheltema, 6a Heereplein, Groningen, The Netherlands.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.
Place: Bâle, Switzerland: Time: September, 1935.

FOREIGN

Royal Society of Medicine, Section for the Study of Disease in Children

President: R. C. Jewesbury, Esq., M.D., 5 Wimpole St., W. 1, London.
Secretary: Dr. Helen Mackay, 28 John St., W. C. 1, London.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:30 p. m.

NATIONAL

American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. A. Graeme Mitchell, Children's Hospital, Cincinnati.
Secretary: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Place: Atlantic City, N. J. Time: June 10-14, 1935.

American Academy of Pediatrics

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Place: New York. Time: June 7-8, 1935.
Region I. Place: New York, Ambassador Hotel. Time: Oct. 19-20, 1934.
Region II. Place: San Antonio, Texas. Time: Nov. 14, 1934.
Region III. Place: Cincinnati. Time: Fall, 1935.
Region IV. Place: Oakland, Calif. Time: November 1934.

American Child Health Association

President: Dr. Samuel McC. Hamill, 1822 Spruce St., Philadelphia.
Secretary: Dr. Philip Van Ingen, 125 E. 71st., New York.

American Hospital Association, Children's Hospital Section

President: Mr. Robert Witham, Children's Hospital, Denver.
Secretary: Miss Agnes O'Roke, Kosair Crippled Children's Hospital, Louisville, Ky.

American Pediatric Society

President: Dr. Borden S. Veeder, 3720 Washington Ave., St. Louis.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.
Place: Wade Park Manor, Cleveland. Time: May 2-4, 1935.

Canadian Society for the Study of Diseases of Children

President: Dr. D. P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary-Treasurer: Dr. R. R. Struthers, 1414 Drummond St., Montreal.
Place: Buffalo, N. Y. Time: June 1935.

Society of Pediatric Research

President: Dr. Joseph Stokes Jr., Children's Hospital, Philadelphia.
Secretary: Dr. A. A. Weech, Babies Hospital, New York.
Place: Atlantic City, N. J. Time: May 1935.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

SECTIONAL

North Pacific Pediatric Society

President: Dr. Armin Rembe, Stimson Bldg., Seattle.
Secretary: Dr. Frank H. Douglass, 1227 Medical and Dental Bldg., Seattle.

Southern Medical Association, Section on Pediatrics

Chairman: Dr. Oliver W. Hill, 301 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. Madison Hines Roberts, 104 Ponce de Leon Ave., N. E., Atlanta, Ga.
Place: San Antonio, Texas. Time: Nov. 13-16, 1934.

STATE

Alabama Pediatric Society

President: Dr. Charles Abbott, 1817 Broad St., Tusaloosa.
Secretary-Treasurer: Dr. Wallace Clyde, Employee's Hospital, Fairfield.
Place: Mobile. Time: April 17-19, 1935.

Georgia Pediatric Society

President: Dr. Benjamin Bashinski, 700 Spring St., Macon.
Secretary-Treasurer: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.
Place: Atlanta. Time: Dec. 13, 1934.

Louisiana State Pediatric Society

President: Dr. John Signorelli, 2000 Tulane Ave., New Orleans.
Secretary-Treasurer: Dr. Edwin A. Socola, 1027 Canal Bank Bldg., New Orleans.
Place: New Orleans. Time: April 29, 1935.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. George Sincerbeaux, 6 William St., Auburn.
Secretary: Dr. John D. Craig, 12 E. 11th St., New York.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Edgar E. Martmer, 749 David Whitney Bldg., Detroit.
Secretary: Dr. C. R. Dengler, 131 W. Michigan Ave., Jackson.
Place: Flint. Time: September 1935.

Mississippi State Pediatric Society

President: Dr. N. C. Womack, Jackson Infirmary, Jackson.
Secretary-Treasurer: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Place: To be designated by Society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. J. A. Henske, 1614 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. J. H. Murphy, 915 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Second Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. J. Buren Sidbury, 15 N. Fifth St., Wilmington.
Secretary: Dr. E. K. McLean, 121 W. Seventh St., Charlotte.
Place: Various children's hospitals. Time: Twice a year.

Oklahoma State Pediatric Society

President: Dr. C. V. Rice, 222 Wall St., Muskogee.
Secretary: Dr. B. H. Nicholson, 301 N. W. Twelfth St., Oklahoma City.
Place: Oklahoma City. Time: May 1935.

Pennsylvania Medical Society, Pediatric Section

Chairman: Dr. Francis T. O'Donnell, 345 North Main St., Wilkes-Barre.
Secretary: Dr. Theodore O. Elterich, 119 S. Highland Ave., Pittsburgh.

South Carolina Pediatric Society

President: Dr. Julian P. Price, Medical Bldg., Florence.
Secretary-Treasurer: Dr. Leland B. Salters, 317 S. Warley Ave., Florence.
Place: Columbia. Time: January 1935.

Tennessee State Pediatric Society

President: Dr. Arthur G. Jacobs, 1193 Madison Ave., Memphis.
Secretary: Dr. Joe T. Smith, 702 Medical Arts Bldg., Knoxville.
Place: Nashville. Time: April 1935.

Texas Pediatric Society

President: Dr. Ramsay H. Moore, 3600 Fairmount St., Dallas.
Secretary-Treasurer: Dr. F. H. Lancaster, Medical Arts Bldg., Houston.
Place: San Antonio. Time: Nov. 13, 1934.

Virginia Pediatric Society

President: Dr. Thomas D. Jones, Medical Arts Bldg., Second and Franklin Streets, Richmond.
Secretary: Dr. W. A. McGee, 616 W. Grace St., Richmond.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. R. C. Hood, 428 W. Pike St., Clarksburg.
Secretary: Dr. Russell C. Bond, 1325 Chapline St., Wheeling.

LOCAL

Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harry M. Greenwald, 499 Ocean Ave., Brooklyn.
Secretary: Dr. Sylvan D. Lazarus, 847 Lincoln Place, Brooklyn.
Place: Medical Society of County of Kings Bldg., 1313 Bedford Ave., Brooklyn.
Time: Third Wednesday of each month from October to May, 8:30 p. m.

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. A. Garvin, Carnegie Medical Bldg., Cleveland.
Secretary: Dr. William M. Champion, 2323 Prospect Ave., Cleveland.
Place: Cleveland Medical Library Bldg., Time: October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. C. V. Mulligan, 17 Walmer Rd., N., Toronto.
Secretary: Dr. T. B. Verner, 170 St. George St., Toronto.

Bronx Pediatric Society

President: Dr. Morris Gleich, 9 Post Ave., New York.
Secretary: Dr. Harry D. Pasachoff, 1560 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

Chicago Pediatric Society

President: Dr. Stanley Gibson, 9503 Prospect Ave., Chicago.
Secretary: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Place: John B. Murphy Memorial Bldg. Time: Third Tuesday of each month.

Dallas County Pediatric Society

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas, Texas.
Secretary: Dr. R. S. Usry, 1835 Garrett Ave., Dallas, Texas.
Place: Bradford Memorial Hospital. Time: 1 p. m., first and third Saturdays of each month.

Detroit Pediatric Society

President: Dr. Earl W. May, 1551 Woodward Ave., Detroit.
Secretary: Dr. W. J. Scott, 5140 Second Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. L. H. Muse, 384 Peachtree St., Atlanta.
Secretary: Dr. T. I. Willingham, 384 Peachtree St., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Frank Lancaster, Medical Arts Bldg., Houston, Texas.
Secretary-Treasurer: Dr. A. A. Little Jr., 817 Holman Ave., Houston, Texas.
Place: Houston Club: Time: Third Monday of each month.

Intermountain Pediatric Society

President: Dr. Helmina Jeidell, 11 Exchange Pl., Salt Lake City, Utah.
Secretary-Treasurer: Dr. Edwin R. Murphy, 9 Exchange Pl., Salt Lake City, Utah.
Place: Salt Lake City, General Hospital. Time: First Thursday of each month, 8 p. m.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1103 Grand Ave., Kansas City.
Secretary: Dr. S. A. Stadler, 6133 Brookside Blvd., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Henry A. Reisman, 148, 88th Ave., Jamaica, L. I.
Secretary-Treasurer: Dr. Edith A. Mittell, 112 Queens Blvd., Forest Hills, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Clyde V. Croswell, 1052 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month, except June, July and August, 8 p. m.

Milwaukee Pediatric Society

President: Dr. F. R. Janney, 1411 Wauwatosa Ave., Wauwatosa, Wis.
Secretary: Dr. John H. Reynolds, 1628 Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New England Pediatric Society

President: Dr. James L. Gamble, 300 Longwood Ave., Boston.
Secretary: Dr. Gerald Hoeffel, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Harry Bakwin, 132 E. 71st St., New York.
Secretary: Dr. Alexander T. Martin, 107 E. 85th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. O. W. Rowe, 205 W. 2nd St., Duluth, Minn.
Secretary: Dr. E. F. Robb, 1801 Lyndale Ave., S. Minneapolis.
Place: Minneapolis. Time: Spring, 1935.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala, Pa.
Secretary: Dr. James E. Bowman, 4091 Comly St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Henry C. Flood, Highland Bldg., Pittsburgh.
Secretary: Dr. E. R. McClusky, 3200 Fifth Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Tuesday, alternate months from October to April, inclusive.

RICHMOND PEDIATRIC SOCIETY

President: Dr. W. A. McGee, 616 W. Grace St., Richmond, Va.
Secretary-Treasurer: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month (except July, August and September).

ROCHESTER PEDIATRIC SOCIETY

President: Dr. H. F. Rowley, 176 S. Goodman St., Rochester, N. Y.
Secretary: Dr. J. M. Parker, 26 S. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Arthur L. Esserman, Republic Bldg., Denver.
Secretary: Dr. Ralph Verploeg, 19th and Gilpin Sts., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. J. V. Cooke, St. Louis Children's Hospital, St. Louis.
Secretary-Treasurer: Dr. Katherine Bain, Beaumont Bldg., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Armin C. Rembe, Stimson Bldg., Seattle.
Secretary: Dr. Frank H. Douglass, Medical-Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Victor E. Stork, 1136 W. Sixth St., Los Angeles.
Secretary: Dr. Howard R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. John F. Sanders, 320 Townsend St., Lansing, Mich.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Place: University Hospital, Ann Arbor, Mich. Time: Nov. 23-24, 1934.

American Journal of Diseases of Children

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TREATMENT OF WHOOPING COUGH WITH AN ACTIVE UNDENATURED ANTIGEN

MINNOLA STALLINGS, M.D.

SAN FRANCISCO

AND

VALERIE C. NICHOLS, B.A.

BERKELEY, CALIF.

CURRENT EPIDEMIC AND MATERIAL

In a previous communication we reported a preliminary study [1] conducted to ascertain the therapeutic value of pertussis antigen prepared according to the method described by Krueger [2] and adapted to Haemophilus pertussis by Krueger, Nichols and Frawley.[3] The preliminary work included two groups of cases, one observed in Fresno, Calif., by Dr. J. M. Frawley and the other seen in the outpatient clinic of the department of pediatrics of the University of California Medical School by one of us (M. S.). The present report details the complete study on the latter group.

The epidemic which we have followed began in December 1932; it was generalized throughout the state of California and was still in progress, although comparatively few cases were developing, at the time of writing (August 1933). The incidence had been 222 reported cases per hundred thousand population. The trend had been from moderate virulence early in the epidemic toward marked virulence over the period from April to August 1933. The mortality for the period of the epidemic, December 1932 to July 1, 1933, was 1.6 reported deaths from pertussis per hundred thousand population.

There were no beds available for the hospitalization of severely ill patients; hence they were treated in the outpatient department or at home. While it was deemed advisable to retain alternate patients for

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From the Department of Pediatrics, University of California Medical School, San Francisco, and the Department of Bacteriology, University of California, Berkeley, Calif.

Dr. Jacques Gray, Assistant Director of Public Health, San Francisco, furnished the epidemiological data. Dr. Francis Scott Smyth and Dr. Bettie U. Harris also assisted in the preparation of this report.

1. Frawley, J. M.; Stallings, M., and Nichols, V. C.: A New Pertussis Antigen, J. Pediat. **4**:179, 1934.

2. Krueger, A. P.: A Method for the Preparation of Bacterial Antigen, J. Infect. Dis. **53**:237, 1933.

3. Krueger, A. P.; Nichols, V. C., and Frawley, J. M.: Proc. Soc. Exper. Biol. & Med. **30**:1097, 1933.

untreated controls, this procedure was not found feasible; parents would not bring in their children unless they believed that active treatment was being carried out. The routine examination consisted of cough plates,[4] frequent studies of the blood picture, careful recording of the history and thorough physical examination. Each patient was seen daily, and the parents were instructed to keep records of the child's progress. The severely ill children were visited in their homes by one of us (M. S.) and assisting nurses. Treatment was begun only when a definite diagnosis was made or when it was deemed advisable to protect contacts in families in which pertussis was already diagnosed.

It would be desirable to have available adequate controls for comparison with the treated group. As noted heretofore, these data could not be obtained under the existing conditions, and in lieu of it we attempted to accumulate statistics regarding patients who were seen by members of the staff of the department of pediatrics of the University of California Medical School. However, these data have the disadvantage of originating with a variety of observers in several different areas, and we cannot see that any detailed analysis of them would be worth while here. It should be noted, however, that in 165 such cases the average duration of severe symptoms was three weeks, and the total average duration of the disease, seven weeks.

The Antigen.—Krueger has recently emphasized the rôle of denaturation reactions in altering the antigenicity of bacteria during the physical and chemical manipulations incident to the preparation of vaccines.[2] In order to obviate this denaturation factor he has devised a technic for physically disrupting live bacterial cells and for putting into solution or suspension the cellular components released by this method. Residual live cells are removed by ultrafiltration,[5] and the filtrate is employed as an antigen. Krueger, Nichols and Frawley[6] employed this technic in the preparation of an active undenatured antigen from Haemophilus pertussis. They showed that this material was capable of immunizing rabbits against lethal doses of virulent Haemophilus pertussis. The clinical evaluation of this antigen presents the difficulties inherent in the study of any therapeutic modality.

Cutaneous Test.—Intradermal injections of 0.1 cc. were administered to 145 children who were not suffering from pertussis and who had not had a previous infection. None of these children showed positive reactions. It was noted early that during the disease a marked erythematous reaction was elicited. These data will be analyzed in a separate article together with the results obtained in the diagnosis of pertussis by means of cough plates.

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4. Sauer, L. W., and Hambrecht, A. B.: Whooping Cough; Early Diagnosis by the Cough Plate Method, J. A. M. A. **95**:263 (July 26) 1930.

5. Krueger, A. P., and Ritter, R. C.: J. Gen. Physiol. **13**:409, 1930.

TABLE 1.—*Results of Treatment with Krueger Undenatured Antigen in Patients with Pertussis*

No.		Age	Sex	Duration of Symptoms When First Seen: Catarrhal Stage	Duration of Symptoms When First Seen: Paroxysmal Stage	Cough Plate: I	Cough Plate: II	Cutaneous Test	Dosage Number of Injections	Symptoms After Treatment: Severe	Symptoms After Treatment: Mild	Results	Comment
1	F. A.	2½ yrs.	F	2 wks.	.....	+	..	+	13	1 wk.	2 wks.	Fair	
2	D. A.	9 yrs.	F	2 wks.	.....	—	+	+	7	.....	1 wk.	Good	
3	J. A.	7 yrs.	M	1 wk.	1 wk.	+	+	+	5	.....	1 wk.	Good	
4	D. A.	4 yrs.	M	1 wk.	.....	—	+	+	6	3 das.	1 wk.	Good	
5	M. A.	38 yrs.	F	2 wks.	.....	+	..	++	17	2 wks.	2 wks.	Fair	
6	Ma. A.	14 mos.	F	1 wk.	4 das.	+	..	+	5	3 wks.	1 wk.	Poor	Inadequate treatment
7	E. A.	2½ yrs.	F	1 wk.	1 wk.	+	..	+	7	2 wks.	2 wks.	Poor	Inadequate treatment
8	M. A.	5½ mos.	M	2 wks.	.....	0*	..	+	12	2 wks.	2 wks.	Poor	
9	M. A.	2½ yrs.	F	2 wks.	1 wk.	+	..	+	5	.....	1 wk.	Good	
10	J. M. A.	2½ yrs.	F	10 das.	.....	+	..	+	14	2 wks.	1 wk.	Fair	Treatment interrupted
11	G. A.	6 yrs.	F	2 wks.	3 wks.	+	+	+	5	1 wk.	1 wk.	Fair	
12	M. A.	2 mos.	F	10 das.	.....	0	..	+	11	1 wk.	2 wks.	Fair	
13	R. A.	17 mos.	M	12 das.	.....	+	..	+	8	4 wks.	1 wk.	Poor	
14	E. B.	20 mos.	M	2 wks.	.....	+	..	+	8	.....	1 wk.	Good	
15	M. M. B.	2½ yrs.	F	2 wks.	.....	+	..	+	14	10 das.	10 das.	Fair	
16	M. B.	adult	F	1 wk.	.....	+	..	++	8	.....	9 das.	Good	
17	V. B.	3 yrs.	F	2 wks.	1 wk.	0	..	+	5	.....	4 das.	Good	
18	G. B.	7 mos.	M	1 wk.	1 wk.	+	..	+	5	.....	4 das.	Good	
19	J. B.	5 yrs.	F	1 wk.	4 das.	+	+	+	9	.....	10 das.	Good	
20	E. B.	14 mos.	F	1 wk.	.....	+	..	+	10	1 wk.	3 das.	Good	
21	A. B.	2 yrs.	F	1 wk.	2 wks.	+	..	+	5	1 wk.	2 wks.	Fair	
22	R. B.	10 mos.	M	1 wk.	.....	+	..	+	5	1 wk.	2 wks.	Fair	Report by telephone; not seen after fifth injection
23	J. B.	21 mos.	F	10 das.	.....	—	..	+	10	1 wk.	2 wks.	Good	
24	B. B.	10 wks.	F	1 da.	.....	0	..	+	8	3 das.	8 das.	Poor	Died; streptococcus pneumonia
25	A. B.	1 yr.	F	1 wk.	.....	0	..	+	6	.....	1 wk.	Good	Whooped twice
26	B. B.	5 mos.	F	2 wks.	1 wk.	0	..	+	10	.....	2 wks.	Good	
27	B. C.	2½ yrs.	M	4 das.	.....	+	..	+	13	1 wk.	1 wk.	Good	
28	F. C.	7 wks.	M	10 das.	.....	0	..	+	6	.....	4 das.	Good	
29	J. C.	3 yrs.	F	8 das.	.....	+	..	+	6	.....	11 das.	Good	
30	C. C.	4 yrs.	M	4 wks.	2 das.	+	..	+	10	3 das.	1 wk.	Good	
31	B. C.	4 yrs.	F	1 wk.	4 das.	+	..	+	10	1 wk.	1 wk.	Good	
32	A. J. C.	2 yrs.	F	2 das.	.....	+	..	+	9	2 wks.	2 wks.	Fair	Much improved; relapse
33	C. C.	6 mos.	M	2 wks.	1 wk.	0	..	+	11	3 das.	1 wk.	Good	
34	C. C.	20 mos.	F	2 wks.	1 wk.	0	..	+	11	3 das.	10 das.	Good	
35	J. C.	4 wks.	F	4 das.	.....	+	..	+	10	4 das.	10 das.	Good	
36	R. C.	21 mos.	M	3 wks.	.....	—	..	+	8	.....	3 wks.	Good	
37	L. C.	5½ yrs.	F	1 wk.	.....	+	..	+	10	.....	7 das.	Good	
38	E. C.	7 yrs.	F	2 wks.	1 wk.	—	—	+	9	3 wks.	1 wk.	Poor	
39	K. C.	2 mos.	M	2 das.	.....	0	..	+	4	.....	2 wks.	Good	
40	A. C.	27 mos.	F	1 wk.	.....	—	+	+	16	2 wks.	1 wk.	Fair	
41	B. D.	3½ yrs.	M	1 wk.	.....	0	..	+	11	1 wk.	2 wks.	Good	
42	J. D.	2½ yrs.	M	1 wk.	.....	0	..	+	11	1 wk.	2 wks.	Good	
43	Wm. D.	5 yrs.	M	3 wks.	2 wks.	—	—	+	6	3 das.	1 wk.	Good	
44	R. D.	7 yrs.	M	10 das.	.....	+	..	+	6	1 wk.	1 wk.	Good	
45	W. D.	5 yrs.	M	2 wks.	.....	—	..	+	6	1 wk.	1 wk.	Good	
46	A. D.	7 yrs.	M	2 wks.	.....	—	+	+	4	.....	4 das.	Good	
47	B. D.	6 yrs.	..	8 das.	.....	+	..	0	7	.....	3 das.	Good	
48	B. D.	2 yrs.	F	3 das.	.....	+	..	+	10	6 das.	6 das.	Good	
49	D. D.	3 yrs.	F	2 das.	.....	—	+	+	10	1 wk.	1 wk.	Good	
50	G. E.	6 yrs.	M	2 wks.	2 das.	+	..	+	4	1 wk.	2 wks.	Good	
51	E. E.	10 mos.	M	1 da.	.....	0	..	+	11	2 wks.	1 wk.	Fair	
52	H. E.	2½ yrs.	F	5 das.	.....	+	..	+	5	.....	5 das.	Good	
53	E. E.	3 yrs.	M	2 das.	.....	—	..	—+	15	2 wks.	2 wks.	Fair	
54	O. E.	6 yrs.	F	2 wks.	.....	+	..	—+	15	2 wks.	2 wks.	Fair	
55	W. F.	5½ yrs.	M	2 wks.	1 wk.	+	..	+	7	.....	1 wk.	Good	
56	F. F.	2½ yrs.	M	1 wk.	.....	—	—	+	4	.....	10 das.	Good	
57	L. F.	1 yr.	F	9 das.	.....	—	—	+	6	1 wk.	2 wks.	Good	
58	L. F.	3½ yrs.	F	1 wk.	.....	0	..	+	5	1 wk.	1 wk.	Good	
59	B. F.	20 mos.	F	2 wks.	.....	0	..	+	5	1 wk.	1 wk.	Good	
60	S. G.	3½ wks.	F	1 wk.	1 wk.	0	..	0	5	1 wk.	1 wk.	Good	
61	B. G.	7 yrs.	F	2 wks.	.....	+	..	+	5	.....	1 wk.	Good	
62	M. G.	5 yrs.	M	1 wk.	.....	+	+	—+	10	1 wk.	1 wk.	Good	Treatment started in the third week

* No cough plate or cutaneous test was made.

TABLE 1.—*Results of Treatment with Krueger Undenatured Antigen in Patients with Pertussis—Continued*

No.		Age	Sex	Duration of Symptoms When First Seen: Catarrhal Stage	Duration of Symptoms When First Seen: Paroxysmal Stage	Cough Plate: I	Cough Plate: II	Cutaneous Test	Dosage Number of Injections	Symptoms After Treatment: Severe	Symptoms After Treatment: Mild	Results	Comment
63	A. H.	3 yrs.	F	1 wk.	.....	+	+	+	5	.....	1 wk.	Good	
64	R. H.	5 yrs.	M	1 wk.	.....	—	—	+	5	.....	1 wk.	Good	
65	S. H.	5½ yrs.	F	2 wks.	.....	+	..	—+	9	10 das.	1 wk.	Fair	
66	A. H.	12 yrs.	M	1 wk.	.....	+	..	+	8	.....	10 das.	Good	
67	J. H.	9 yrs.	M	2 wks.	.....	—	+	+	8	.....	10 das.	Good	
68	M. H.	4½ yrs.	F	4 das.	.....	+	..	+	7	1 wk.	1 wk.	Good	
69	J. H.	2 yrs.	M	1 da.	.....	+	..	—+	7	.....	3 das.	Good	
70	R. H.	16 mos.	M	4 das.	.....	+	..	+	6	1 wk.	.....	Good	
71	C. I.	2 yrs.	M	2 wks.	.....	+	..	+	10	3 wks.	.....	Poor	
72	H. J.	4 yrs.	F	1 wk.	.....	—	+	—	4	1 wk.	10 das.	Good	
73	T. J.	2 yrs.	M	1 wk.	.....	+	+	+	8	1 wk.	1 wk.	Good	
74	P. J.	6 yrs.	F	2 wks.	1 wk.	—	+	+	11	4 das.	1 wk.	Good	
75	B. J.	4 yrs.	F	10 das.	.....	0	..	0	4	.....	1 wk.	Good	
76	B. J.	8 wks.	M	1 wk.	.....	0	—	0	5	4 wks.	.....	Poor	Inadequate treatment
77	J. K.	16 mos.	M	1 wk.	.....	0	..	0	3	.....	3 das.	Good	
78	D. K.	6 yrs.	F	2 wks.	3 das.	+	..	+	10	1 wk.	11 das.	Good	
79	D. K.	Adult	M	3 wks.	2 wks.	+	—	+	11	1 wk.	1 wk.	Good	
80	R. K.	25 yrs.	F	2 wks.	3 wks.	—	—	+	9	1 wk.	1 wk.	Good	
81	W. K.	3½ yrs.	M	10 das.	.....	—	+	+	10	1 wk.	3 das.	Good	
82	S. K.	22 mos.	F	3 wks.	1 wk.	+	..	—+	13	3 wks.	.....	Poor	Treatment interrupted
83	B. K.	4 wks.	M	2 das.	.....	0	..	0	14	3 wks.	.....	Poor	Treatment interrupted
84	B. K.	5 yrs.	M	1 wk.	.....	+	..	+	9	1 wk.	1 wk.	Good	
85	D. K.	6 yrs.	F	2 wks.	.....	+	..	+	11	1 wk.	1 wk.	Good	
86	D. K.	8 yrs.	F	2 wks.	1 wk.	+	..	+	11	1 wk.	1 wk.	Good	
87	D. K.	7 yrs.	M	2 wks.	.....	+	..	+	10	1 wk.	1 wk.	Good	
88	W. L.	6 yrs.	M	2 wks.	.....	+	..	+	8	1 wk.	1 wk.	Good	
89	F. L.	7½ yrs.	M	2 wks.	.....	—	..	+	8	1 wk.	1 wk.	Good	
90	R. L.	3 wks.	M	1 da.	.....	0	..	—+	13	3 wks.	.....	Poor	Treatment interrupted
91	H. L.	3 yrs.	M	2 wks.	2 wks.	0	..	+	6	.....	1 wk.	Good	
92	D. L.	2 yrs.	M	3 wks.	2 wks.	—	+	+	9	.....	10 das.	Good	
93	E. L.	3 yrs.	F	3 das.	.....	—	+	+	5	.....	5 das.	Good	
94	G. L.	3½ yrs.	M	4 das.	.....	—	—	+	5	.....	5 das.	Good	
95	P. L.	7½ mos.	F	1 da.	.....	+	..	+	5	.....	5 das.	Good	
96	R. L.	8 yrs.	M	2 wks.	1 wk.	—	—	+	5	.....	1 wk.	Good	
97	W. L.	6 yrs.	M	2 wks.	.....	—	..	+	5	.....	1 wk.	Good	
98	V. L.	8 yrs.	F	3 das.	.....	+	..	+	6	1 wk.	1 wk.	Good	
99	B. L.	9 yrs.	F	2 wks.	.....	0	..	+	6	1 wk.	1 wk.	Good	
100	B. L.	4 yrs.	M	2 wks.	.....	0	..	+	6	1 wk.	2 wks.	Fair	
101	D. H.	3½ yrs.	F	1 wk.	.....	—	—	+	9	2 wks.	2 wks.	Poor	
102	A. H.	5½ yrs.	F	1 wk.	1 wk.	+	..	+	9	2 wks.	2 wks.	Poor	
103	V. L.	4 yrs.	F	1 wk.	.....	+	..	+	8	1 wk.	2 wks.	Good	Inadequate treatment
104	K. L.	18 mos.	M	3 das.	.....	+	..	+	5	2 wks.	1 wk.	Fair	Inadequate treatment
105	M. L.	18 mos.	F	2 wks.	.....	+	+	+	10	2 wks.	1 wk.	Fair	
106	R. L.	6 yrs.	M	2 wks.	1 wk.	+	..	+	5	.....	1 wk.	Good	
107	O. L.	3 yrs.	F	1 wk.	.....	+	..	+	10	1 wk.	1 wk.	Good	
108	M. M.	3 yrs.	F	2 wks.	.....	0	..	+	9	3 das.	1 wk.	Good	
109	L. M.	6½ yrs.	M	2 wks.	.....	+	..	+	10	1 wk.	3 das.	Good	
110	B. M.	12 yrs.	F	8 das.	.....	+	..	0	5	.....	3 das.	Good	
111	M. M.	8 yrs.	F	3 das.	.....	0	..	0	5	.....	3 das.	Good	
112	J. M.	3 yrs.	M	2 das.	.....	+	..	0	5	.....	2 das.	Good	
113	R. M.	3 yrs.	M	1 wk.	.....	+	..	+	6	1 wk.	1 wk.	Good	
114	J. M.	1 yr.	F	4 das.	.....	+	..	+	10	2 wks.	2 wks.	Fair	
115	P. M.	1 yr.	M	1 da.	.....	0	..	+	5	.....	3 das.	Good	
116	D. M.	3 yrs.	M	1 da.	.....	0	..	+	5	.....	3 das.	Good	
117	R. M.	2 yrs.	M	2 wks.	2 wks.	—	+	++	6	.....	1 wk.	Good	
118	T. M.	6 mos.	M	2 wks.	.....	0	..	—	4	.....	1 wk.	Good	
119	N. M.	14 mos.	M	1 wk.	.....	0	+	—+	8	2 wks.	1 wk.	Fair	
120	C. M.	6½ yrs.	M	11 das.	.....	+	..	+	5	.....	1 wk.	Good	
121	E. M.	5½ yrs.	F	2 wks.	1 wk.	+	—	+	8	1 wk.	1 wk.	Good	
122	J. M.	5 yrs.	F	2 wks.	.....	—	+	+	11	1 wk.	1 wk.	Good	
123	B. M.	6 mos.	F	2 wks.	.....	+	..	+	10	2 wks.	1 wk.	Fair	
124	B. M.	15 mos.	M	2 wks.	1 wk.	+	..	+	6	1 wk.	1 wk.	Good	
125	J. Mc.	3 mos.	M	1 wk.	.....	—	+	+	11	2 wks.	2 wks.	Fair	Treatment discontinued; relapse
126	E. Mc.	4 yrs.	F	2 wks.	.....	—	..	+	5	1 wk.	1 wk.	Good	Severe when treatment was started
127	A. Mc.	1 yr.	M	2 das.	.....	+	+	—+	14	1 wk.	2 wks.	Good	Treatment discontinued; relapse; treatment reinstituted

* No cough plate or cutaneous test was made.

TABLE 1.—*Results of Treatment with Krueger Undenatured Antigen in Patients with Pertussis—Continued*

No.		Age	Sex	Duration of Symptoms When First Seen: Catarrhal Stage	Duration of Symptoms When First Seen: Paroxysmal Stage	Cough Plate I	Cough Plate II	Cutaneous Test	Dosage Number of Injections	Symptoms After Treatment: Severe	Symptoms After Treatment: Mild	Results	Comment
128	B. Mc.	2 yrs.	F	1 wk.	.....	—	..	—	8	8 das.	1 wk.	Good	
129	M. Mc.	adult	M	12 das.	.....	—	+	+	10	1 wk.	2 wks.	Good	
130	M. Mc.	adult	F	2 wks.	1 wk.	0	..	+	7	3 wks.	.....	Poor	Treatment inadequate
131	C. N.	3 yrs.	F	1 wk.	.....	0	..	+	5	.....	3 wks.	Good	
132	C. N.	2 yrs.	M	3 das.	.....	+	..	+	4	.....	3 wks.	Good	
133	D. N.	6 yrs.	F	1 wk.	3 das.	+	..	+	4	.....	5 das.	Good	
134	L. N.	5½ yrs.	F	2 wks.	2 wks.	0	..	+	5	.....	2 wks.	Good	
135	L. N.	3 mos.	F	2 wks.	.....	—	..	—	6	.....	6 das.	Good	
136	K. N.	.....	..	3 das.	.....	+	..	0	4	.....	6 das.	Good	
137	J.McK.	3 mos.	F	10 das.	.....	+	—	+	6	.....	1 wk.	Good	
138	G.McK.	7 yrs.	M	10 das.	.....	+	..	+	6	.....	1 wk.	Good	
139	K. O.	4 yrs.	F	2 wks.	2 wks.	+	+	+	12	10 das.	1 wk.	Fair	
140	S. O.	11 mos.	F	2 wks.	.....	+	..	+	6	1 wk.	1 wk.	Good	Treatment started in the fifth week of the disease
141	G. P.	3½ yrs.	F	5 das.	.....	+	..	+	12	1 wk.	3 wks.	Fair	
142	R. P.	2 mos.	M	1 wk.	.....	+	..	—+	12	1 wk.	3 wks.	Fair	
143	J. P.	6 mos.	F	1 wk.	.....	+	..	+	10	.....	2 wks.	Good	
144	R. P.	5½ yrs.	M	2 das.	.....	+	+	+	11	.....	2 wks.	Good	
145	D. P.	5½ yrs.	M	1 wk.	.....	—	..	+	11	1 wk.	1 wk.	Good	
146	C. P.	4 mos.	M	1 da.	.....	—	+	+	17	.....	18 das.	Good	
147	M. P.	6 yrs.	F	1 wk.	.....	—	..	+	11	.....	16 das.	Good	
148	R. P.	4 yrs.	M	3 das.	.....	+	..	+	11	4 das.	14 das.	Good	
149	M. P.	adult	F	1 wk.	.....	—	..	+	7	.....	10 das.	Good	
150	L. P.	2 yrs.	F	2 wks.	.....	0	..	0	11	.....	2 wks.	Good	
151	A. R.	1½ yrs.	F	4 wks.	2 wks.	—	..	+	4	.....	1 wk.	Good	
152	B. R.	4 yrs.	F	4 wks.	.....	+	..	+	4	.....	1 wk.	Good	
153	E. G.	2 yrs.	F	10 das.	.....	+	..	+	6	.....	2 wks.	Good	
154	L. R.	1 yr.	F	2 wks.	1 wk.	—	..	+	5	.....	10 das.	Good	
155	A. R.	2 yrs.	M	2 wks.	.....	0	..	+	7	.....	1 wk.	Good	
156	C. R.	3 yrs.	F	2 wks.	.....	0	..	0	8	.....	1 wk.	Good	
157	S. R.	4 yrs.	M	2 wks.	.....	0	..	—	11	.....	2 wks.	Good	
158	B. R.	4 yrs.	F	1 wk.	.....	+	+	+	11	10 das.	2 wks.	Fair	Diabetic
159	R. R.	1 yr.	F	1 wk.	.....	+	—	+	5	.....	1 wk.	Good	
160	E. R.	8 yrs.	F	1 wk.	.....	+	..	—+	12	1 wk.	2 wks.	Good	
161*	V. B.	2½ yrs.	F	4 das.	.....	+	..	+	14	3 wks.	1 wk.	Poor	
162	A. R.	4½ yrs.	M	4 das.	.....	—	..	+	6	.....	.....	Good	
163	T. R.	7 yrs.	M	1 wk.	.....	—	..	+	7	10 das.	1 wk.	Fair	
164	E. R.	5½ yrs.	M	4 das.	.....	—	—	+	5	.....	2 das.	Good	
165	J. R.	2 yrs.	F	2 wks.	.....	—	+	+	12	1 wk.	2 wks.	Good	
166	D. R.	3½ yrs.	M	5 das.	.....	+	..	+	5	.....	3 wks.	Good	
167	L. R.	13 yrs.	F	2 wks.	.....	+	..	+	6	1 wk.	2 wks.	Good	
168	I. R.	13 yrs.	F	2 wks.	.....	+	..	+	6	2 wks.	2 wks.	Good	
169	F. R.	15 yrs.	M	1 wk.	.....	+	..	+	6	1 wk.	1 wk.	Good	
170	R. R.	16 yrs.	M	.....	1 da.	—	—	—	6	.....	1 da.	Good	
171	C. R.	16 mos.	F	1 wk.	.....	+	..	+	12	1 wk.	2 wks.	Good	Family of five children, seen early; positive cough plate in one case
172	D. R.	8 yrs.	F	2 wks.	1 wk.	—	..	+	9	.....	17 das.	Good	
173	A. R.	10 yrs.	F	2 wks.	.....	—	..	++	9	.....	2 wks.	Good	
174	A. R.	4 yrs.	M	1 wk.	.....	—	..	++	9	.....	2 wks.	Good	
175	C. R.	9 yrs.	F	2 wks.	.....	—	..	+++	9	.....	2 wks.	Good	
176	H. R.	13 mos.	F	3 wks.	1 wk.	+	..	++	5	1 wk.	2 wks.	Fair	
177	W. R.	4 yrs.	M	2 das.	.....	+	+	+	4	.....	5 das.	Good	
178	A. R.	4½ yrs.	M	1 wk.	2 wks.	—	+	++	12	.....	17 das.	Good	
179	F. R.	14 mos.	M	2 wks.	1 wk.	+	..	—+	17	2 wks.	1 wk.	Fair	Had severe secondary anemia at onset
180	A. R.	3 yrs.	M	2 wks.	1 wk.	+	..	—+	14	.....	3 wks.	Good	
181	J. S.	28 mos.	F	1 wk.	.....	—	..	—	8	.....	3 das.	Good	Whooped only once
182	B. S.	7 wks.	M	1 wk.	.....	0	..	—	11	.....	7 das.	Good	White cell count, 18,240; lymphocytes, 80%
183	B. S.	10 mos.	M	1 wk.	.....	0	..	+	10	.....	4 das.	Good	

* No cough plate or cutaneous test was made.

TABLE 1.—*Results of Treatment with Krueger Undenatured Antigen in Patients with Pertussis—Continued*

No.		Age	Sex	Duration of Symptoms When First Seen: Catarrhal Stage	Duration of Symptoms When First Seen: Paroxysmal Stage	Cough Plate: I	Cough Plate: II	Cutaneous Test	Dosage Number of Injections	Symptoms After Treatment: Severe	Symptoms After Treatment: Mild	Results	Comment
184	M. S.	4 yrs.	F	5 das.	.....	+	+	+	10	4 das.	1 wk.	Good	Treatment delayed until appearance of of severe symptoms, third week
185*	J.L.S.	3½ yrs.	F	10 das.	.....	+	..	++	18	8 das.	2 wks.	Good	Treatment, 0.1 cc. 5 days; severe symptoms; dosage increased
186*	J.A.S.	5 mos.	F	1 da.	.....	+	..	+	18	2 wks.	1 wk.	Fair	Treatment, 0.1 cc. 5 days; severe symptoms; dosage increased
187	I.M.S.	4⅔ yrs.	F	4 das.	.....	+	..	+	16	.....	2 wks.	Good	
188	P. S.	3 yrs.	M	1 da.	.....	0	..	++	15	2 wks.	1 wk.	Fair	
189	N. S.	6 yrs.	F	2 wks.	.....	+	..	+	11	1 wk.	2 wks.	Good	
190	R. St.	2 yrs.	M	1 wk.	.....	+	..	+	5	.....	5 das.	Good	
191	Rm.St.	3½ yrs.	F	1 wk.	.....	—	..	—	5	.....	1 wk.	Good	Brother, positive cough plate
192	N. S.	6 yrs.	F	2 wks.	1 wk.	—	..	+	4	.....	4 das.	Good	
193	B. S.	5½ yrs.	M	2 wks.	.....	+	..	+	10	3 das.	1 wk.	Good	
194	A. S.	3 yrs.	M	10 das.	.....	—	..	+	10	.....	12 das.	Good	
195	K. S.	5 yrs.	M	1 da.	.....	+	..	++	12	1 wk.	2 wks.	Good	
196	I. S.	3 yrs.	F	2 das.	.....	+	..	++	15	1 wk.	2 wks.	Good	
197	M.J.S.	7 yrs.	F	5 das.	.....	+	..	+	16	1 wk.	2 wks.	Good	
198	E. V.	4 yrs.	M	1 wk.	.....	0	..	+	5	.....	1 wk.	Good	
199	J. V.	8 mos.	M	5 das.	.....	0	..	+	5	.....	1 wk.	Good	
200	T. G.	19½ yrs.	M	10 das.	.....	—	..	+	8	1 wk.	1 wk.	Good	
201	R. T.	1 mo.	F	10 das.	.....	0	..	0	6	1 wk.	2 wks.	Good	
202	W. T.	18 mos.	M	10 das.	.....	+	..	0	6	1 wk.	2 wks.	Good	
203	D. T.	1 yr.	M	10 das.	.....	+	..	+	12	2 wks.	2 wks.	Fair	
204	J. W.	2 mos.	M	1 wk.	.....	—	..	—	6	.....	1 wk.	Good	White cell count, 10,120; lymphocytes, 79%
205	H. W.	4 yrs.	M	1 wk.	.....	—	..	+	6	.....	2 wks.	Good	
206	B. W.	6 yrs.	M	2 wks.	1 wk.	—	..	+	6	.....	2 wks.	Good	
207	F. W.	7 mos.	F	2 wks.	.....	+	..	++	14	2 wks.	2 wks.	Fair	
208	H. W.	2½ yrs.	M	2 wks.	1 wk.	+	..	+	10	1 wk.	2 wks.	Good	
209	M. W.	25 yrs.	F	2 wks.	1 wk.	—	..	+	6	3 das.	1 wk.	Good	
210	G. Y.	12 mos.	M	5 das.	.....	—	+	+	4	.....	10 das.	Good	
211	H. W.	3 yrs.	M	1 wk.	.....	+	..	+	7	1 wk.	2 wks.	Good	
212	T.Mc.	7½ yrs.	M	9 das.	.....	+	..	+	4	1 wk.	2 wks.	Good	
213	K. K.	4 yrs.	F	2 das.	.....	—	..	0	5	10 das.	1 wk.	Poor	Severe symptoms started ten days after injection
214	N. K.	18 mos.	F	2 wks.	1 wk.	+	..	0	7	1 wk.	2 wks.	Good	
215	B. S.	4½ yrs.	M	2 wks.	1 wk.	0	..	0	6	.....	2 wks.	Good	
216	J. S.	3 yrs.	F	1 wk.	.....	0	..	0	6	4 das.	1 wk.	Good	
217	J. C.	3 yrs.	F	2 wks.	.....	0	..	0	12	2 wks.	3 wks.	Poor	
218	B. C.	18 mos.	M	1 wk.	.....	0	..	0	15	3 wks.	2 wks.	Poor	
219	H. S.	4½ yrs.	F	2 wks.	1 wk.	0	..	0	7	4 das.	1 wk.	Good	
220	B. S.	2 yrs.	M	4 das.	.....	0	..	0	5	.....	1 wk.	Good	
221	C.B.H.	5½ yrs.	M	2 wks.	3 das.	+	..	0	6	3 das.	10 das.	Good	
222	R. H.	4 yrs.	M	2 wks.	3 das.	+	+	0	7	2 wks.	1 wk.	Fair	Inadequate treatment
223	J. H.	5 yrs.	M	2 wks.	3 wks.	+	..	0	5	1 wk.	2 wks.	Good	
224	M. B.	4 yrs.	F	2 wks.	.....	+	..	0	8	1 wk.	2 wks.	Good	
225	B. C.	6 mos.	M	1 da.	.....	0	..	0	8	1 wk.	2 wks.	Good	
226	M. S.	11 yrs.	F	2 wks.	.....	—	—	+	15	12 das.	2 wks.	Fair	
227	B. I.	6 yrs.	M	2 wks.	.....	+	..	+	8	2 wks.	2 wks.	Fair	
228	D. S.	3 mos.	F	10 das.	.....	+	..	+	4	1 wk.	.....	Good	
229	J. K.	5 yrs.	M	2 wks.	.....	+	..	—	6	.....	.....	Good	
230	E. K.	2½ yrs.	F	1 da.	.....	—	+	..	0	.....	.....	Good	
231	J. A.	30 yrs.	..	10 das.	.....	—	..	0	3	.....	3 das.	Good	
232	D. C.	3 yrs.	M	6 das.	.....	+	..	..	8	.....	2 wks.	Good	

* No cough plate or cutaneous test was made.

Therapeutic Dosage.—Three general plans of administration were successively developed:

1. The patients in this group were given an initial dose of 0.1 cc., the amount being increased 0.1 cc. daily up to 1 cc. The latter amount was continued until the symptoms abated. Severe conditions were treated with daily doses beginning with 0.2 cc. and increasing by 0.2 cc. each day until a total of 1 cc. was reached.

2. In this group the initial dose consisted of 0.25 cc. and was followed by 0.5 cc., 0.75 cc. and, finally, 1 cc., the antigen being administered every other day. In general this plan was adequate for mild cases, but in severe cases it was noticeable that the coughing was much more severe on the day on which no injections were given.

TABLE 2.—*Results of Treatment in Contacts*

No.		Age	Sex	Cough Plate I	Cough Plate II	Cutaneous Test	Dosage Number of Injections	Symptoms After Treatment: Severe	Mild	Results
1	G. M.	10 yrs.	M	0*	0	0	4	None	None	Good
2	D. V.	2½ yrs.	M	0	0	0	4	None	None	Good
3	O. J.	10 mos.	M	0	0	0	5	None	None	Good
4	R. F.	5½ yrs.	F	0	0	0	4	None	4 days	Good
5	D. D.	9 yrs.	F	0	0	0	4	.....	4 days	Good
6	C. C.	10 yrs.	F	0	0	0	6	None	None	Good
7	W. C.	4 yrs.	M	0	0	0	4	None	1 week	Good
8	G. C.	4 yrs.	F	0	0	..	5	None	None	Good
9	A. D.	Adult	F	0	0	0	6	None	2 weeks	Good
10	A. E.	Adult	F	0	0	0	6	None	None	Good
11	W. F.	5 yrs.	M	0	0	0	8	None	4 days	Good
12	B. Y.	2½ yrs.	F	0	0	0	5	None	2 days	Good
13	J. N.	4 yrs.	M	—	..	0	..	None	4 days	Good
14	C. C.	4½ yrs.	M	0	0	0	5	None	None	Good
15	A. C.	21 mos.	F	—	..	0	6	None	None	Good
16	E. P.	4 yrs.	F	0	0	0	5	None	None	Good
17	W. S.	5 mos.	F	0	0	0	5	None	None	Good
18	G. P.	1 yr.	F	0	0	0	5	None	None	Good

* No cough plate or cutaneous test was made.

3. A daily dose of 0.1 cc. without increase was tried in a group of 10 cases. In 8 children the symptoms progressed, and the dosage stated under plan 1 was instituted.

Contact Dosage.—The small group of children who were treated prophylactically were given 0.2 cc., 0.4 cc., 0.6 cc., 0.8 cc. and 1 cc. every other day; the last dose of 1 cc. was repeated. The patients in whom symptoms developed were given one or more additional injections.

Criteria of Therapeutic Efficacy.—Results were considered good when severe symptoms subsided in one week or less after treatment was begun. In this connection it should be stated that in our judgment three or four mild paroxysms daily did not constitute a severe picture. Other factors considered in the patient's response were the general physical condition, appetite and sleep.

The results were considered fair when severe symptoms abated within from ten days to two weeks after the institution of treatment. The general factors mentioned were considered in this light also.

When symptoms continued over two weeks, with the general condition of the patient affected by lack of sleep and with loss of weight and other unfavorable manifestations, the result was considered poor.

It should be borne in mind that these patients were seen at least every other day and for the most part every day in the clinic or at home so that there is a minimum reliance on the mothers' reports. Considerable weight was given to the child's general appearance from day to day.

COMMENT

We are not unaware of the difficulties involved in the clinical evaluation of suggested remedies for whooping cough. The disease is vari-

TABLE 3.—*Summary of Tables 1 and 2*

	Results	Number of Cases	Percentage of Group
Catarrhal stage	Good	96	78.7
	Fair	17	13.9
	Poor	9	7.4
Paroxysmal stage	Good	84	76.4
	Fair	17	15.4
	Poor	9	8.2
	Total	232	
Total percentages	Good		77.6
	Fair		14.7
	Poor		7.7
Contact group	Good (no symptoms)	11	
	Good (developed slight symptoms)	7	

able, and in this series we lack the strict academic control group which would be desirable as a basis of comparison. As noted, our attempts to utilize every other case as a control interfered with obtaining sufficient clinical material, and it was found to be an impracticable measure under the existing circumstances. Our only measure of control, therefore, is that furnished us by the data of competent observers on the staff of the department of pediatrics. Their observations on 165 patients not treated with this antigen give the following relevant figures:

1. The total average duration of the disease was seven weeks.

2. The average minimum figure for severe symptoms was three weeks. This in a general way offers a characterization of the nature of the epidemic, and together with the data on incidence and mortality already cited indicates an epidemic of moderate severity.

Table 1 shows that in a group of 232 patients the average total duration of symptoms was four weeks and the average duration of severe symptoms, ten days. In this group the analysis shown in table 3 obtains.

It is clear, then, that so far as end-results are concerned little if any difference is evident between the institution of treatment in the catarrhal stage and that in the paroxysmal stage. It appears that approximately 77 per cent of good results are secured in either case. The percentage of fair and of poor results in the two groups is approximately identical. To settle the question of there being any advantage in starting treatment early a much larger series will be required, but we have the distinct clinical impression that undenatured antigen is as effective in the paroxysmal as in the catarrhal stage.

The mechanism of action in the infected person has not been experimentally determined, but observations on intelligent adults with severe pertussis show in from two to three hours an alleviation of symptoms lasting about twenty to twenty-four hours. Symptoms recur after this time and are relieved by the next injection. In this respect the mechanism appears to be a desensitization, while if we postulate the establishment of active immunity we should expect a prolonged therapeutic response after the requisite number of doses has been given, whereas in practice the period of relief from symptoms is relatively brief and recurs after each injection.

We have on record a few cases which shed light on the efficacy of the antigen. For example, in one case antigen which had been denatured by accident was used in large doses without result, although the patient had been getting along nicely before the denaturation occurred. When the denatured sample was replaced by an undenatured preparation, an immediate favorable reaction with complete alleviation of symptoms followed (table 1, E. K., no. 230).

It will be noted in table 3 that we observed 18 contact cases, that is, 16 children and 2 young adults who definitely had not had whooping cough and who were exposed to the disease in their own families. In all these instances the contact was intimate and prolonged, and each patient received from four to six injections of antigen beginning with 0.2 cc. and increasing to 1 cc. In 11 children no symptoms developed, while 7 contracted a very light form of the disease. We conclude from this small contact group that the results were good in 100 per cent of the cases, but this conclusion must be qualified because of the small number seen and the probable natural variation in susceptibility.

CONCLUSIONS

1. During an epidemic of pertussis generalized throughout California a series of 232 patients were treated with undenatured pertussis antigen in the outpatient clinic of the department of pediatrics of the University of California Medical School. These patients were under close observation; the diagnosis was based on symptomatology, blood count and cough plates.

2. Our criteria were as follows: good results, abatement of severe symptoms within one week or less; fair results, abatement within two weeks; poor results, persistence of severe symptoms over two weeks. On this basis we observed approximately 78 per cent of good, 14 per cent of fair and 8 per cent of poor results in patients seen during both the catarrhal and the paroxysmal stage of the disease.

3. Of 18 patients with no previous history of pertussis and with intimate exposure to the disease in their own families, 11 showed no symptoms, and 7 had extremely light symptoms.

BLOOD PICTURE IN EXPERIMENTAL WHOOPING COUGH

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No definite theory had been established as to the cause of the leukocytosis and lymphocytosis which accompany whooping cough until several years ago Fukushima,[1] by a chemical analysis, proved that the Bordet-Gengou bacillus contains abundance of fat and lipoid which if injected into animals cause leukocytosis and lymphocytosis. Sauer and Hambrecht [2] also proved the appearance of a similar blood picture in experimental whooping cough in monkeys infected with the Bordet-Gengou bacillus. These facts lead us to assume that the leukocytosis and lymphocytosis which accompany whooping cough are merely a biologic reaction of the organism caused by infection with pertussis bacilli.

As a result of a recent experiment in which we infected young monkeys and puppies with Bordet-Gengou bacilli and made a clinical and pathologico-anatomic study as well as differential counts of the leukocytes, it was ascertained that the blood picture mentioned would appear not only in monkeys but in puppies. Moreover, we made some observations on the significance of the symptoms of this disease.

PROCEDURE

Freshly cultured Bordet-Gengou bacilli suspended in saline solution were sprayed per os into the laryngeal cavity of four young monkeys (Macacus rhesus, weighing from 1,500 to 3,500 Gm.) and two puppies (weighing from 2,000 to 5,000 Gm.) once every day or every other day. Three or four sprayings given in this way succeeded in infecting all of the animals. In addition, four young monkeys and four puppies were made victims of a natural infection by being exposed intimately to the artificially infected animals.

To test whether or not the animals were infected by pertussis bacilli, paroxysmal cough was induced, the expectorated mucus was examined for Bordet-Gengou bacilli, and the blood picture was observed. After the animals were killed or had died of the disease, the respiratory organs were examined for the presence of pertussis bacilli. To identify pertussis bacilli, each time the serum of a person convalescent from pertussis was employed for a test of the complement-fixation reaction.

From the department of pediatrics, Manchuria Medical College.

1. Fukushima, M.: Orient. J. Dis. Infants **3**:10, 14 and 43, 1928.

2. Sauer, L. W., and Hambrecht, Leonora: Experimental Whooping Cough, Am. J. Dis. Child. **37**:732 (April) 1929.

RESULTS

Leukocytosis and lymphocytosis were observed in seven of the eight monkeys and in all of the six puppies suffering from either artificial or natural infection. This proves that when they are infected by pertussis bacilli not only monkeys but puppies can acquire the blood picture characteristic of whooping cough. We have already reported, on the strength of our numerous experiences on human pertussis, that this blood picture, in the absence of complications, is so well correlated with the development of the clinical stage of the process that it is possible with ease and accuracy to diagnose as well as to determine the stage of the disease; in case of complications, such as severe bronchitis or pneumonia, leukocytosis loses its significance so far as the diagnosis

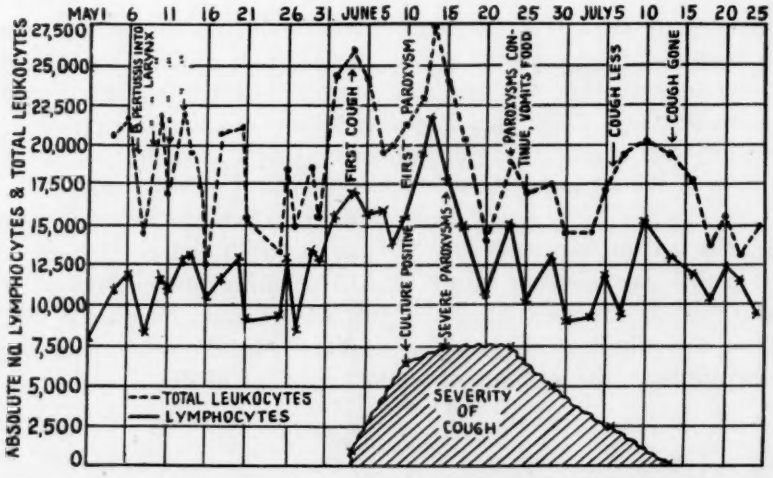

Chart 1 (monkey 2).—Curves showing leukocytosis and lymphocytosis in an animal artificially infected with pertussis.

of the disease and the determination of the stage are concerned, for these complications almost constantly are accompanied by leukocytosis, which conceals the leukocytosis and lymphocytosis characteristic of whooping cough. Even in this case, however, if the absolute number of lymphocytes is determined it is often easy to diagnose whooping cough and determine its stage for the reason that when complications creep in at the paroxysmal stage and leukocytosis become manifest, the absolute number of lymphocytes increases tremendously, whereas in leukocytosis caused by complications in the early stage of pertussis or in the decline the absolute number of lymphocytes does not increase so much. Therefore, if one wants to make use of the blood picture for diagnosing whooping cough and determining its stage it is much more justifiable and safe to rely on the absolute number of lymphocytes

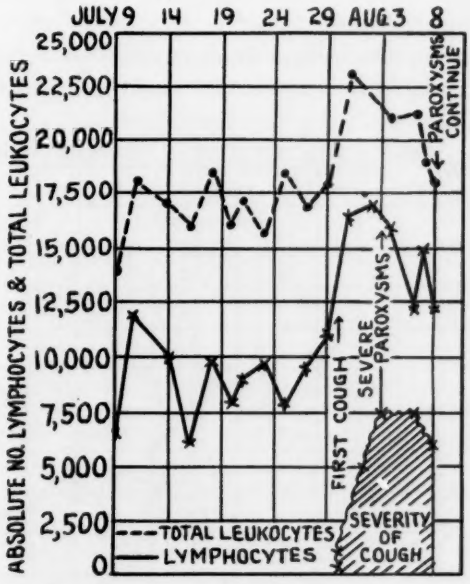

Chart 2 (monkey 5).—Curves showing leukocytosis and lymphocytosis in an animal naturally infected with pertussis.

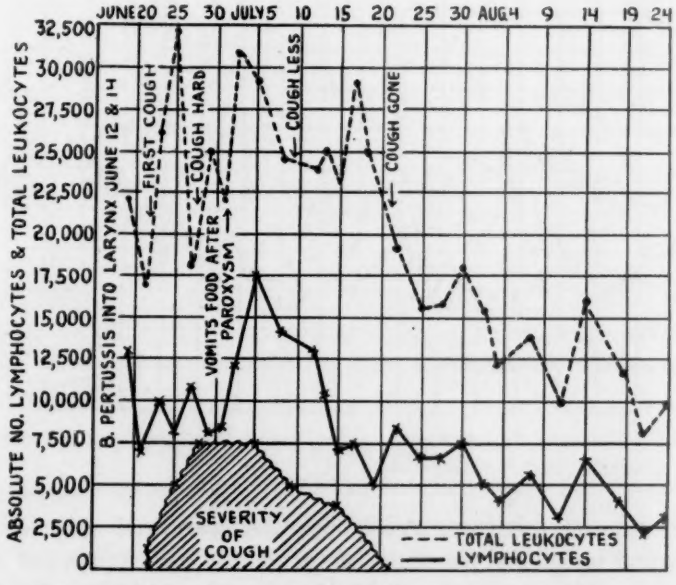

Chart 3 (puppy 10).—Curves showing leukocytosis and lymphocytosis in an animal artificially infected with pertussis.

than on the total number of leukocytes and the percentage of lymphocytes as usually determined.

Let this principle now be applied to the blood picture in experimental whooping cough as produced by us. In monkeys 2 (artificial infection)

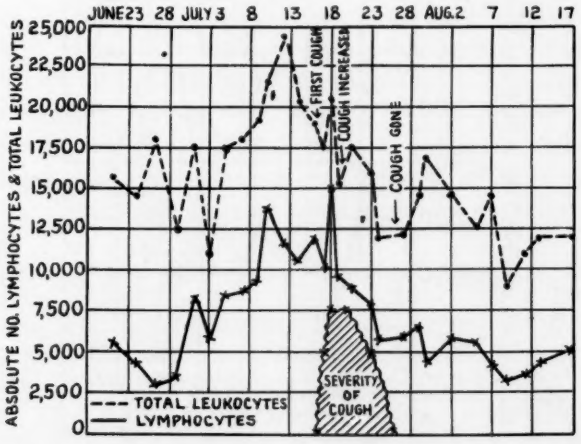

Chart 4 (puppy 11).—Curves showing leukocytosis and lymphocytosis in an animal naturally infected with pertussis.

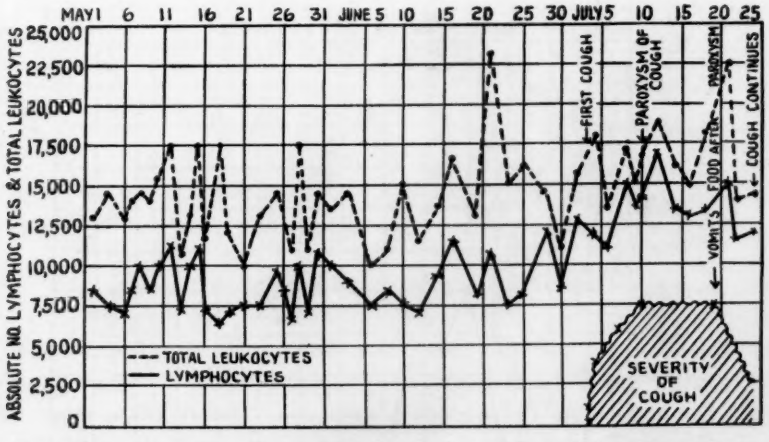

Chart 5 (monkey 7).—Curves showing leukocytosis and lymphocytosis in an animal naturally infected with pertussis.

and 5 (natural infection) and puppies 10 (artificial infection) and 11 (natural infection), the clinical stage and the leukocytosis and lymphocytosis were fairly well correlated with each other in their courses. However, leukocytosis and lymphocytosis do not necessarily keep pace with each other. For instance, in monkey 7 (natural infection) in the

early stage of the disease the increase in the lymphocyte count coincided with the clinical stage of whooping cough far better than did that of the total leukocyte count. Moreover, in puppy 10 (artificial infection), in the decline stage of whooping cough, the lymphocyte count decreased gradually in a regular manner, while the total leukocyte count fluctuated too irregularly to signify the real progress of the disease; for example, the total leukocyte count on July 17 was likely to lead one

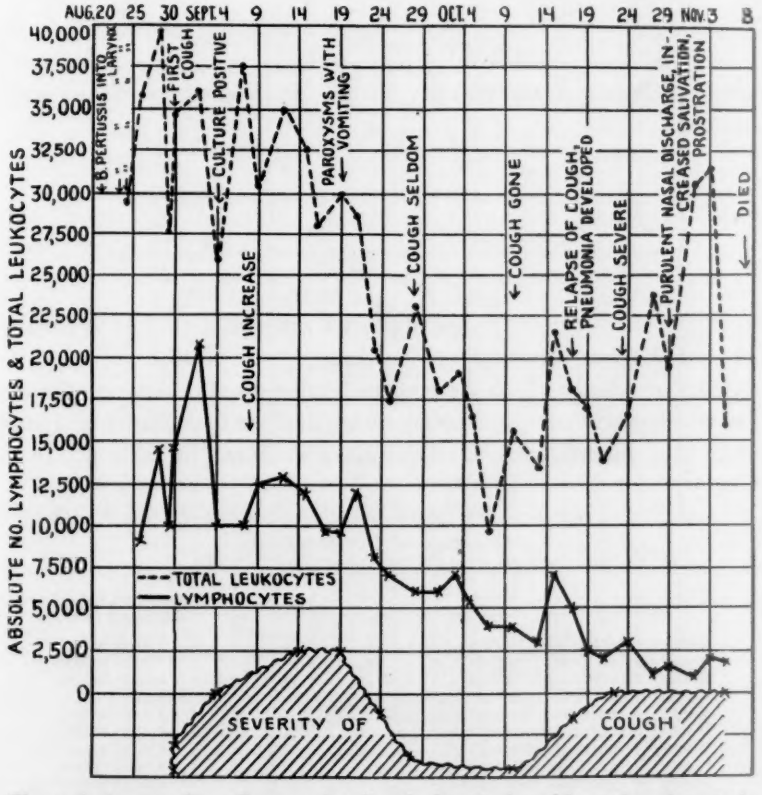

Chart 6 (puppy 9).—Curves showing leukocytosis without lymphocytosis in pneumonia developing as a complication in the declining stage of pertussis in an animal artificially infected.

to believe that the disease was at the peak of severity, whereas one glance at the absolute number of lymphocytes was sufficient to show that the course was approaching its end.

With regard to pneumonia pertussis complicating the case of puppy 9 (artificial infection) can be brought up, in which at the end of the seventh week of the disease the total numbers of both leukocytes and lymphocytes were found decreased, but when pneumonia developed,

the total leukocyte count rapidly increased while the number of lymphocytes remained unaffected, which was proof that the disease was in either the terminal or the decline stage. As none of the laboratory animals in this experiment contracted pneumonia at the paroxysmal stage, we are without proof of the behavior of the absolute number of lymphocytes in such a case; but according to our experience with human pertussis, as already stated, not only should the total leukocyte count increase greatly, but the total lymphocyte count should increase to a fair extent.

The following tabulation shows the time elapsing between the infection and the appearance of lymphocytosis in the artificially infected monkeys, counting from the day of the first spraying of the saline suspension:

Monkey No.	Days
1	22
2	26
3	19
4	22

This shows that lymphocytosis appeared after a period of incubation which lasted from three to four weeks.

Next the relation, both in monkeys and puppies, between the date of the development of spontaneous cough and the appearance of lymphocytosis was investigated. The results are shown in table 1. In six

TABLE 1.—*Time Between Development of Spontaneous Cough and Appearance of Lymphocytosis*

Animal	Development of Lymphocytosis in Relation to Cough
Monkey 1 (artificial infection)	5 days before
Monkey 2 (artificial infection)	2 days before
Monkey 3 (artificial infection)	1 day before
Monkey 4 (artificial infection)	Same day
Monkey 5 (natural infection)	1 day after
Monkey 6 (natural infection)	4 days after
Monkey 7 (natural infection)	6 days after
Puppy 9 (artificial infection)	4 days before
Puppy 10 (artificial infection)	6 days before
Puppy 11 (natural infection)	7 days before
Puppy 12 (natural infection)	Same day
Puppy 13 (natural infection)	4 days after
Puppy 14 (natural infection)	15 days after

out of thirteen cases lymphocytosis appeared before the development of spontaneous cough, from which one can conclude that lymphocytosis appears after a certain period of incubation and is not necessarily influenced by the paroxysmal cough. Therefore, to insist that lymphocytosis is a mechanical effect of cough is not correct, but the theory which explains it as a biologic reaction caused by an infection with pertussis bacilli is well justified.

In spite of the statement of Sauer and Hambrecht [3] that in human as well as animal pertussis, leukopenia in the early stage of the disease is a feature of the blood picture, we failed to notice clearly such an

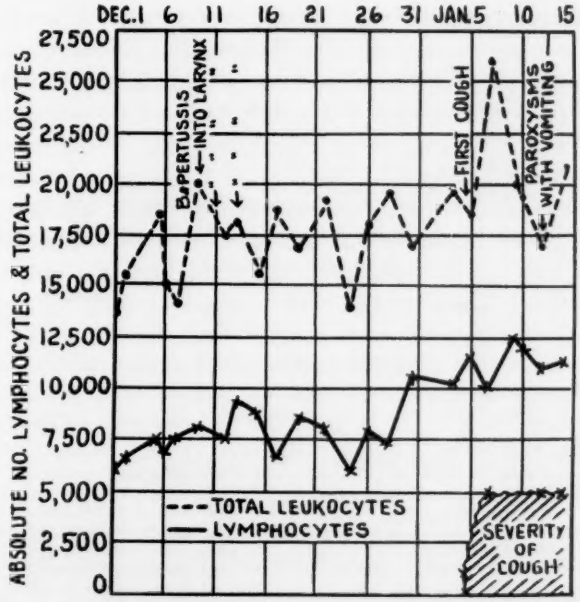

Chart 7 (monkey 1).—Curves showing lymphocytosis even at the catarrhal stage of experimental pertussis but no leukopenia.

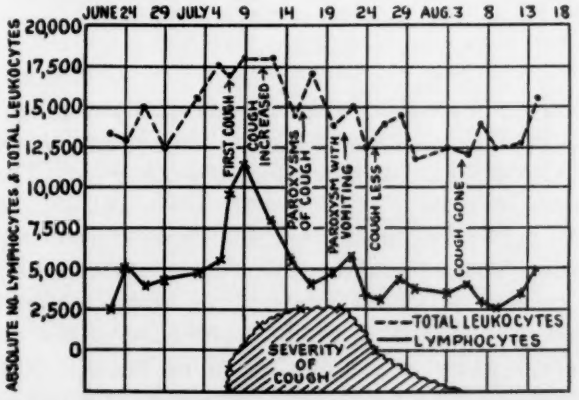

Chart 8 (puppy 12).—Curves showing absence of leukopenia in the early stage of pertussis in an animal naturally infected.

3. Sauer, L. W., and Hambrecht, Leonora: Whooping Cough: The Blood Picture with Special Reference to Early Observations, Am. J. Dis. Child. **41**:1327 (June) 1931.

initial leukopenia in any of the forty-five cases of human pertussis in which an observation of the blood picture was made at the catarrhal stage, but in 42 per cent of the cases leukocytosis and lymphocytosis were manifest.

Table 2 shows the dates on which examinations of the blood were begun in the experimental animals. Examination of the blood was carried out once every day or every other day for a long time before the appearance of lymphocytosis and cough, but not once was leukopenia noticed. For this reason, we are not convinced of the occurrence of initial leukopenia in whooping cough. On the other hand, leukocytosis and lymphocytosis at the catarrhal stage of the disease, which have been described by many authors and which we had noticed in human pertussis, were observed in approximately half of the cases of experimental whooping cough, as has been stated.

TABLE 2.—*Time at Which Examinations of Blood Were Begun*

Animals	Examination of Blood Begun
Monkey 5 (natural infection)	22 days before development of cough
Monkey 6 (natural infection)	28 days before development of cough
Monkey 7 (natural infection)	61 days before development of cough
Puppy 11 (natural infection)	17 days before development of cough
Puppy 12 (natural infection)	17 days before development of cough
Puppy 13 (natural infection)	14 days before development of cough
Puppy 14 (natural infection)	17 days before development of cough
Monkey 1 (artificial infection)	Day of inoculation with pertussis bacilli
Monkey 2 (artificial infection)	Day of inoculation with pertussis bacilli
Monkey 3 (artificial infection)	Day after inoculation with pertussis bacilli
Monkey 4 (artificial infection)	Day after inoculation with pertussis bacilli
Puppy 9 (artificial infection)	Day of inoculation with pertussis bacilli
Puppy 10 (artificial infection)	Day of inoculation with pertussis bacilli

CONCLUSION

We succeeded in producing experimental whooping cough by means of infection in eight young monkeys and six puppies. Except in one mild case, leukocytosis and lymphocytosis were observed. The symptom appeared after from three to four weeks of incubation, often before the development of paroxysmal cough, and therefore is not a mechanical effect of cough but a biologic reaction caused by infection with the pathogenic bacillus. After the infection and before the appearance of lymphocytosis, no leukopenia could be proved. For the diagnosis of whooping cough and the determination of its stage, it is much more profitable to depend on the absolute number of lymphocytes than on the total leukocyte count and the percentage of lymphocytes, especially when complications are present.

TYPHOID PARATYPHOID THERAPY IN IDIOPATHIC EPILEPSY

A CLINICAL AND EXPERIMENTAL STUDY

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Of the diseases in which the etiology, pathogenesis and treatment are on an infirm and unscientific foundation, epilepsy stands preeminent. In the past a great deal has been written on the subject, and many interesting observations have been recorded by capable clinicians and neurologists; yet despite this voluminous literature, and despite a vast amount of experimental work that has been done, the conception of this disease has not been materially enhanced in the past fifty years. The etiology and the pathogenesis of this disease are as obscure today as they were a century ago.

REVIEW OF LITERATURE

In 1881, William Gowers [1] expressed the view that epilepsy is a disease of the gray matter and has no uniform seat, and that the cause of the convulsive seizure may be a subtle disturbance in the cellular physiology of the brain rather than a gross lesion. The conception of this disease today remains the same. No uniform gross lesions have been found in the brain, and microscopic studies on brains of patients that died from this or other diseases have proved disappointing. The lesions found are not constant, and may be the result rather than the cause of the seizures. Lennox and Cobb [2] in their authoritative monograph concluded that there is no constant anatomic lesion in epilepsy and that only a minority of patients with extensive cerebral pathologic lesions have fits. They postulate the view that some unknown constitutional element is the basic underlying cause and that almost any lesion, plus the unknown X, which may be functional instability, may result in epilepsy. Various theories have been advanced to explain the mechanism of a seizure, but these will not be discussed here.

The greatest recent advance in the knowledge of epilepsy was the demonstration that changes in the physicochemical processes in the body, and presumably therefore in the tissues of the brain, may modify sei-

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From the Department of Pediatrics, Hospital for Joint Diseases, and Beth David Hospital. [Service of Dr. Jacob Sobel.]

1. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Diseases: Their Causes, Symptoms and Treatment, London, J. & A. Churchill, 1881.

2. Lennox, W. G., and Cobb, S.: Epilepsy, from Standpoint of Physiology and Treatment, Medicine **7**:105 (May) 1928.

zures. It has been shown that changes, such as those involving the respiratory function of the brain cells, those disturbing the ionic equilibrium of the brain cells, or those that have to do with the regulation of the water and acid-base balance of the tissues may definitely delay or precipitate epileptic seizures. A defective mechanism in the control of the semipermeability of the membranes of the brain cells has also been suggested. Recently McQuarrie [3] reiterated the same view. He based this conception on the observation of the close correlation between the magnitude of the lecithin-cholesterol ratio in the blood plasma and the occurrence of seizures, the ratio being 25 to 100 per cent higher during the period of the day when the seizures occurred than at other times.

The introduction of the ketogenic diet in the treatment of this disease by Wilder [4] in 1921 was an outgrowth of the physicochemical theories underlying this malady. This diet has been a definite step forward in helping to control the seizures. It was based on the observation that conditions tending to make the blood more alkaline, such as overventilation of the lungs, short periods of anoxemia or ingestion of alkalis, favor the occurrence of seizures, whereas procedures which tend to produce a mild acidosis, such as fasting, the use of the ketogenic diet, administration of carbon dioxide or the ingestion of large doses of acid-forming salts, tend to prevent or alleviate the manifestations of the disease. Helmholz and Keith,[5] reporting on 171 patients that were treated with the ketogenic diet, stated that this diet would free 31 per cent of the patients from attacks and improve an additional 23 per cent. McQuarrie and Keith [6] in their thorough researches pertaining to the relation of a disturbed acid-base equilibrium of the blood plasma and the occurrence of seizures stated that their data do not indicate that this acid-base disturbance is the only or even the main factor involved. They added: "On the contrary, it seems probable to us that this abnormality is merely incidental to a more basic disturbance in the metabolism of the brain cells or in the physicochemical processes concerned with the functions of the surface membranes of the cells."

The dehydration treatment as applied to this disease rests on similar physicochemical theories. It followed the pioneer work of Rowntree [7]

3. McQuarrie, I.: Treatment of Epilepsy in Children, Journal-Lancet **52:** 301 (May 1) 1932.

4. Wilder, R. M.: The Effect of Ketonemia on the Course of Epilepsy, Bull. Mayo Clinic **2:**307 (July 27) 1921.

5. Helmholz, H. F., and Keith, H. M.: Eight Years' Experience with the Ketogenic Diet in the Treatment of Epilepsy, J. A. M. A. **95:**707 (Sept. 6) 1930.

6. McQuarrie, I., and Keith, H. M.: Experimental Study of Acid-Base Equilibrium in Children with Idiopathic Epilepsy, Am. J. Dis. Child. **37:**261 (Feb.) 1929.

7. Rowntree, L. G.: Water Intoxication, Arch. Int. Med. **32:**157 (Aug.) 1923.

and Fay.[8] Many favorable reports of this treatment appear in the literature, notably one by McQuarrie.[9] However, the beneficial results have been challenged by Pagniez,[10] Cobb,[11] Riley,[12] Fetterman and Kumin,[13] and Wilson and Limberger.[14]

That fever has a definite effect on the physicochemical processes of the body and body metabolism is well known. That intercurrent febrile diseases may have a definite and more or less permanent effect on the seizures of epilepsy has been recognized by past generations. Such references are frequently encountered in the earliest medical records. There is frequent reference in the literature to Hippocrates'[15] statement that acute fevers may influence epilepsy both favorably and unfavorably. In 1854 Delasiauve[16] published his observation as to the effects of febrile diseases on epilepsy. He concluded that practically all severe acute illnesses suspend or weaken the frequency of the epileptic seizures, particularly in young subjects. This modification, he stated, was more or less lasting. Some patients, however, were made worse by these intercurrent ailments. At the closing of the last century Séglas,[17] Beckhaus,[18] Pellissier[19] and Friedländer[20] made similar observations on extensive collections of cases. In 1909, Hamilton[21] studied the effects of typhoid fever on 11 cases of epilepsy. Of this number, 9 patients showed a distinct improvement, the condition of 1 remained

8. Fay, Temple: Some Factors in Mechanical Theory of Epilepsy, Am. J. Psychiat. **8**:783 (March) 1929.

9. McQuarrie, Irvine: Epilepsy in Children, Am. J. Dis. Child. **38**:451 (Sept.) 1929.

10. Pagniez, P. H.: Le rôle de l'hydration dans l'épilepsie, Presse méd. **38**: 1574 (Nov. 19) 1930.

11. Cobb, Stanley: Causes of Epilepsy, Arch. Neurol. & Psychiat. **27**:1245 (May) 1932.

12. Riley, H. A., in discussion on Fremont-Smith, Frank: The Influence of Fluid Intake on the Intracranial Pressure in Man, Arch. Neurol. & Psychiat. **28**: 240 (July) 1932.

13. Fetterman, J. L., and Kumin, H. J.: Dehydration in Epilepsy, J. A. M. A. **100**:1005 (April 1) 1933.

14. Wilson, G., and Limberger, W. A.: The Use of Dehydration in Epilepsy, J. A. M. A. **101**:110 (July 8) 1933.

15. Hippocrates, quoted by Friedländer.

16. Delasiauve, L. J. F.: Traité de l'épilepsie, Paris, V. Masson, 1854.

17. Séglas, J.: The Influence of Intercurrent Diseases on the Course of Epilepsy, Thèse de Paris, 1881.

18. Beckhaus, E.: Ueber den Einfluss intercurrenter Krankheiten und physiologischer Processe auf die Epilepsie, Ann. d. städt. allg. Krankenh. zu München (1890-1892), 1894, p. 187.

19. Pellissier, J.: De l'influence des maladies infectieuses intercurrentes sur la marche de l'épilepsie, Thèse de Montpellier, 1898.

20. Friedländer, A.: Ueber den Einfluss des Typhus abdominalis auf das Nervensystem, Berlin, S. Karger, 1901.

21. Hamilton, A. S.: Effect of Intercurrent Disorders on Pre-Existing Epilepsy, J. A. M. A. **53**:1902 (Dec. 4) 1909.

unchanged and 1 died of status epilepticus in the midst of the attack of typhoid fever. He concluded that the effect of typhoid was usually favorable, except for occasional cases in which the influence was negative or unfavorable. Clark and Sharp [22] studied the effects of measles and erysipelas on epilepsy; Gordon [23] and Maillard [24] the effects of influenza on epilepsy. In 1930 Guthrie [25] made a thorough study of intercurrent febrile diseases in 200 cases of epilepsy at the Munson State Hospital. He concluded that respiratory diseases, such as influenza, pneumonia or pertussis, had only a slight effect on the frequency of the seizures, whereas the nonrespiratory diseases, such as mumps, measles, scarlet fever, chickenpox, erysipelas, diphtheria and tonsillitis, were definitely beneficial, there being a 17 per cent reduction in the number of convulsions during the month following the acute illness as compared with the month before the acute illness.

The recent success of malarial therapy in dementia paralytica has stimulated research into the effect of similar treatment in epilepsy. Thus, Rodríguez Arias [26] treated 2 patients with epilepsy by malarial inoculations. He permitted a daily rise of temperature for twelve days. There were no seizures during the twelve days of fever nor for two months following the fever. After that period convulsions began again, but they were less refractory to medical treatment. He also quoted Aguglia and D'Abundo who treated 4 epileptic patients with malarial inoculations. These were free from seizures for three months. Spagnoli [27] treated 6 patients having epilepsy with malarial inoculations with less favorable results. Mendel [28] reported 2 cases of epilepsy in adults that followed attacks of malaria. His report tends to discourage the use of this type of fever therapy in epilepsy. Edgeworth [29] attempted the use of a 5 per cent solution of peptone intravenously in increasing doses, once weekly, with fair results. In 1932 Rodriguez Arias [30] reported the use of typhoid vaccine intravenously. He began with

22. Clark, L. P., and Sharp, E. A.: Influence of Measles and Erysipelas upon Epilepsy, M. News **77**:853, 1900.

23. Gordon, A.: Influenza and Epilepsy, M. Rec. **40**:942, 1921.

24. Maillard, M. G.: Influenza and Epilepsy, Am. J. Clin. Med. **30**:798 (Nov.) 1923.

25. Guthrie, R. H.: Influence of Intercurrent Febrile Disorders on Pre-Existing Epilepsy, Arch. Neurol. & Psychiat. **24**:753 (Oct.) 1930.

26. Rodríguez Arias, B.: Effects of Malaria Therapy in Essential Epilepsy, Rassegna internaz. di clin. e terap. **9**:673 (Aug.) 1928.

27. Spagnoli, B.: Esperimente malarici negli epilettici, Gior. di psichiat. e di neuropath. **60**:169, 1932.

28. Mendel, K.: Epilepsie und Malaria, Med. Klin. **22**:1770 (Nov. 12) 1926.

29. Edgeworth, F. H.: Intravenous Protein Therapy in Epilepsy, Brit. M. J. **2**:780, 1920.

30. Rodríguez Arias, B., and Pons-Balmes, J.: Quelques considérations sur la pyrétothérapie de l'épilepsie, Rev. neurol. **1**:1364, 1932.

200,000,000 bacteria, at intervals of five to seven days, gradually increasing the dose. He did not report his work in detail. However, he cautions against the slight danger of precipitating the condition of status epilepticus.

AUTHOR'S TREATMENT WITH TYPHOID-PARATYPHOID VACCINE

The observations of my co-workers and myself on the beneficial effects of intercurrent febrile diseases on the course of certain cases of epilepsy in children and our recent experience in the use of intravenous

Types of Cases Studied and Results of Treatment

Case	Age	Sex	Diagnosis	Frequency of Attacks	Duration	Comment
1 M. K.	3½ yrs.	Boy	Borderline case of grand mal and petit mal	15 to 25 times per day	18 mos.	Seizures lasted 5 to 15 sec., during which time child would lose consciousness and fall; child was on a ketogenic diet for 6 mos. prior to treatment, seizures being reduced to 4 or 6 per day; diet was continued for six mos. after the treatment was stopped; no recurrences in two yrs.
2 B. F.	14 yrs.	Boy	Grand mal	1 to 3 times per wk.	3 mos.	No recurrence for past 18 mos.
3 F. B.	19 yrs.	Girl	Grand mal	2 to 3 times per wk.	8 yrs.	On the ketogenic diet at one time for 3 mos. without improvement; no attacks while under treatment, but seizures recurred on return home, with customary frequency and severity; no improvement
4 L. N.	10 yrs.	Girl	Grand mal	Once in 3 mos.	8½ yrs.	Low grade moron; no recurrences for past 14 mos.
5 A. D.	10 yrs.	Boy	Grand mal	Twice per mo.	5 yrs.	No recurrences for past 12 mos.
6 H. C.	12 yrs.	Boy	Grand mal	Once every 4 to 6 wks.	6 mos.	No recurrences for past 7 mos.

injections of typhoid-paratyphoid vaccine in cases of chorea stimulated us to try the same treatment in epilepsy. This investigation was based on the hypothesis that the fever is the effective factor in the treatment to be described; that these febrile reactions produce certain physicochemical changes in the fluids and tissues of the body, and presumably, therefore, of the brain cells also; and that these changes have a favorable effect on the seizures. This study began in 1931, and up to the present time we have treated 6 patients. Although the number of patients thus far treated has been too limited to warrant definite conclusions or recommendations, the results, nevertheless, have been sufficiently interesting to warrant this preliminary report, and to encourage us and others, in its further use.

Our plan of study was at first clinical but later our scope widened, as we began to examine the blood for direct evidence of chemical changes resulting from these injections. These findings will be reported separately. We limited our cases to the so-called essential type of epilepsy. Cases showing any definite pathologic lesions of the brain were rejected. We also attempted to select only those patients in whom the seizures were more or less definitely established. The table shows in brief form the type of cases studied.

Typhoid-paratyphoid vaccine was chosen because a sufficient dose invariably produces a sharp febrile reaction even when given daily, and is a simple, cheap and safe method of producing fever. Sutton [31] has proved that a vaccine composed of typhoid bacilli alone does not produce fever if the injections are given at intervals of less than five to seven days, and that not every case responds to high fever.

PROCEDURE

The technic employed and closely followed was that described by Sutton [31] in the treatment of chorea minor. New York City Health Department typhoid-paratyphoid vaccine was given intravenously at the elbow if possible or, in rare instances, in the jugular vein. The vaccine contains 1,000,000 Bacillus typhosus, 750,000,000 Bacillus paratyphosus A, and 750,000,000 Bacillus paratyphosus B, per cubic centimeter. We started with 0.1 cc. and increased 0.1 cc. daily for seven consecutive days. The first dose of 0.1 cc. invariably produced a sharp febrile reaction, the temperature reaching 103 to 105 F. Succeeding doses, however, occasionally had to be modified. If the reaction was too severe with the first dose, and the temperature became too high, reaching 105 to 107 F., the same dose was repeated the next day. Again, if the rise in temperature was not sufficiently high after having increased the dose 0.1 cc., an increase of 0.2 cc. was tried the following day. The reaction began about twenty minutes after the injection. There was a chill lasting about thirty minutes. The temperature then started to rise, reached its peak in about four hours, and was back to normal in about six to eight hours. Occasionally the temperature was elevated the next day. When this happened the same dose was repeated, or no injection was given. In some cases cyanosis occurred at the onset of the chill, but this passed off shortly. Occasionally there was vomiting, but no other untoward effects were noted. After the chill was over, some children complained of a headache or pain in the eyeballs, but generally they were fairly comfortable. Occasionally herpes labialis appeared and, rarely, an urticarial eruption. We gave our injections around 9 a. m., so as to secure an undisturbed night's sleep. The treatment was carried on for seven days. This seven day period was chosen arbitrarily. Outside of nursing care and rest in bed, nothing was done. No medication was administered. The diet was light but plentiful. There were no restrictions in the carbohydrates, except in case 1, and fluids were given ad libitum. The children remained in bed for forty-eight hours after the treatment was over, and were then placed on a regular diet. All cases showed a mild leukocytosis, 12,000 to 15,000, and occasionally a trace of acetone in the urine.

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31. Sutton, Lucy Porter: The Treatment of Chorea by the Induction of Fever, J. A. M. A. **97**:299 (Aug. 1) 1931.

COMMENT

The evaluation of any method of treatment in a disease as complex as epilepsy is unsatisfactory. The disease is much too variable in its manifestations, severity and frequency of attacks to permit definite conclusions. One must recognize that many children who have had convulsions remain free from seizures for months or even years without any medication, special treatment or care. If a few such young patients were grouped together and a form of treatment elaborated, misleading conclusions might be drawn. Every factor that is known to be related to seizures should be given due consideration. I repeat that the number of cases reported here is very limited, but the results have been sufficiently striking to warrant serious consideration, and I hope that this report will stimulate further study in larger groups.

Epilepsy is essentially a disease of childhood and young adults. Although it occurs at all ages it usually begins before the subject is 20 years old. It is, therefore, more closely related to the disorders of childhood than to those of adult life. Experience has shown that children and young adults who have shown manifestations of this disease for short periods respond to any form of treatment more satisfactorily than those who have been sufferers for many years. On this account, greater emphasis should be given to the treatment of epilepsy during childhood than to its treatment in later life.

An analysis of the cases reveals that 4 were of long standing and 2 of shorter duration and these might be grouped as incipient. With the exception of the patient in case 3, they all responded favorably, and there were no recurrences from the time the treatment was instituted to date, these periods ranging from seven months to two years. Of the 6 patients treated, 5 were children and 1 a young adult. The latter was the only one not influenced by the treatment. All patients received one course of treatment, with the exception of the fourth who received two courses at an interval of two months. We thought it advisable to repeat the treatment because the first course was not entirely satisfactory on account of the small size of the patient's superficial veins, which resulted in the vaccine occasionally being injected subcutaneously. Under such circumstances there could be no febrile reaction. There were no changes in the diet, no medication given and no limitation of fluids. All patients showed traces of acetone in their urine for one or two days. The first patient, who had been on a ketogenic diet and had given a positive acetone reaction prior to the treatment, showed also diacetic acid during the treatment. In this case we continued the ketogenic diet for six months after the treatment.

The possible advantages of this method of treatment over that of the ketogenic diet would seem to be that it is shorter, simpler and easier to carry out. Very often, after a short trial, parents decide that there is

no use in continuing the diet, especially if there is no marked improvement. The same applies to the fasting or dehydration treatments. With the first patient, it was used in conjunction with the ketogenic diet. We succeeded in stopping the seizures completely, whereas we were not able to do this with the ketogenic diet alone.

SUMMARY

Six patients with epilepsy have been treated with intravenous injections of typhoid-paratyphoid vaccine as a means of producing fever. Of these, 5 were children, and 1 a young adult. The results in all the children thus far have been good. There were no recurrences of seizures after periods of from seven months to two years from the institution of treatment. The one failure was in the case of a young adult. The treatment is simple and safe and appears to have definite advantages over the ketogenic diet and the dehydration treatment. It may be used to supplement the ketogenic diet in those cases in which the diet does not completely stop the seizures.

IODINE AND THYROID HYPERPLASIA

I. THE IODINE CONTENT OF HUMAN SKIMMED MILK FROM GOITROUS AND NONGOITROUS REGIONS

R. G. TURNER, PH.D.
ASSISTED BY MINA Z. WEEKS
DETROIT

A systematic study of the iodine content of human milk during the period of lactation may enlighten one's course in combating or preventing thyroid hyperplasia. The following report is a step in this direction.

LITERATURE

The ideas expressed in the literature on thyroid disease are so varied and confusing that it is difficult to form a definite and concise conclusion regarding the functions and mechanism involved. Further, examination of the literature reveals little regarding the iodine content of mother's milk and its variations during the period of lactation. Most of the studies reported have been on colostrum.

Maurer and Diez [1] (1926) saponified colostrum with 25 per cent potassium hydroxide. After evaporation and ashing they extracted with alcohol and determined the iodine content colorimetrically after the method of von Fellenberg.[2] They found that colostrum has a high iodine value with decided quick falls. They claimed that its iodine value is higher than that of cow's milk, especially during the early colostral period. This confirmed the findings of von Fellenberg,[2] who found a decrease of approximately 80 per cent on the fifth day of lactation. Findings for normal human colostrum in 2 cases were reported as shown in table 1.

In a later report Maurer and Ducrue [3] (1928) found that 0.6 mg. of potassium iodide given each day did not change the quantity of milk secreted by mothers, but increased the iodine content far above the

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1. Maurer, E., and Diez, S.: München. med. Wchnschr. **73**:17, 1926.
2. von Fellenberg, T.: Ergebn. d. Physiol. **25**:176, 1926.
3. Maurer, E., and Ducrue, H.: München. med. Wchnschr. **75**:249, 1928.

normal. One specimen of normal human milk had an iodine content of 2.6 micrograms per hundred cubic centimeters. Scharrer and Schwaibold [4] (1929), experimenting on cows, concluded that the iodine content of milk is more or less proportional to the quantity of iodine ingested. With 200 mg. of iodine per day, fed as potassium iodide, the average expected increase was 30 micrograms per hundred cubic centimeters. They found that the butter obtained from cow's milk is practically iodine-free, while the cheese obtained contains about one third of the total iodine content of the milk.

Evvard [5] (1928) fed iodine to breeding ewes causing the milk to be high in iodine for a brief period. Increasing doses of iodide given ewes decreased the size of the thyroid gland in the new-born lambs and increased the percentage of iodine in the gland, thus preventing goiter in these lambs. Evvard's figures for the iodine in ewe's milk are much greater than those published for cow's milk, averaging 240

TABLE 1.—*Iodine Content of Normal Human Colostrum*

Day of Lactation	Case 1	Case 2	Cow's Milk
1	24.0*	21.0	16.5
2	12.7	13.5	3.5
3	11.1	8.0	3.0
4	5.4	5.5	2.5
5	4.3	4.6	2.5

* Expressed in micrograms per hundred cubic centimeters.

micrograms per hundred cubic centimeters or 24 parts per million. Oertel [6] (1931) found considerable iodine in the colostral milk of goats. After the colostral period the iodine decreased to a minimum. Goats from which the thyroid glands have been extracted show a low iodine content in the colostral milk.

Hercus and Roberts [7] (1927) found that the iodine content of milk from goitrous women is definitely lower than that of milk from nongoitrous women. They reported that immediately after parturition the iodine content of the milk of nongoitrous women was 8 micrograms per hundred cubic centimeters, dropping to 2.5 micrograms two months later and finally to 1.6 micrograms in the fourth and fifth months. In the milk of goitrous women seven days after parturition the iodine content was only 1.6 micrograms. They found the initial iodine content of cow's milk to be 2 micrograms per hundred cubic centimeters.

4. Scharrer, K., and Schwaibold, J.: Biochem. Ztschr. **213**:32, 1929.
5. Evvard, J. M.: Endocrinology **12**:539, 1928.
6. Oertel, R.: Milchwirtsch. Liter. **52**:429, 1931.
7. Hercus, C. E., and Roberts, K. C.: J. Hyg. **26**:49, 1927.

McClendon, Remington and von Kolnitz [8] (1930) determined traces of iodine in samples of dried skimmed cow's milk. For skimmed milk they reported amounts varying from 142 to 1,300 parts per billion, which is equivalent to from 14.2 to 130 micrograms per hundred grams of dried skimmed milk. Assuming the total solids of cow's milk to be 13 per cent, the approximate iodine value of the liquid milk would be from 1.8 to 16.9 micrograms per hundred cubic centimeters. The latter value is 6 or 8 times greater than that found for normal cow's milk and human milk by foreign investigators. Such conflicting results cannot be accounted for other than by the use of unreliable methods for the estimation of the iodine content or by the possibility that the iodine content of foods in different parts of the country varies to such a degree as to cause these discrepancies. The findings reported by McClendon and his co-workers included only a few cases, and the investigations were not carried through the entire period of lactation.

Our investigation includes a study of the iodine content of milk from mothers in Detroit—a goitrous region—and from mothers in Boston—a nongoitrous region. The object was to determine the value of iodine in the milk of these mothers at varying intervals during the mature period of lactation. It is important to know whether the nursing infant of a mother living in the Middle West consumes as much iodine as the nursing infant of a mother in a nongoitrous region. The values of the calcium and inorganic soluble phosphates were determined with that of the iodine as a basis for comparison in the fluctuations during the different stages of lactation.

It has been shown by numerous investigators that the calcium level of mother's milk is lowest during the first two weeks of lactation, gradually rising to a maximum during the first four months and then falling slowly during the remaining course of lactation. Telfer [9] reported that the percentage of phosphorus in milk runs parallel to that of calcium, increasing to a maximum after the first two weeks and then decreasing gradually. Contrary to this, Widdows and her associates [10] found that the percentage of phosphorus remains almost constant after the fourth month, while Schloss [11] reported decrease and an increase after the third month and a gradual decrease to the eleventh month.

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8. McClendon, F.; Remington, R. C., and von Kolnitz, H.: J. Am. Chem. Soc. **52**:541, 1930; **53**:1245, 1931.

9. Telfer, S. V.: Biochem. J. **18**:809, 1924.

10. Widdows, S. T.; Lowenfeld, M. B., and Taylor, E. I.: Biochem. J. **24**:327, 1930.

11. Schloss, E.: Monatschr. f. Kinderh. **10**:499, 1911.

MATERIAL

Subjects.—The milk for analysis was obtained from women at the Detroit Mothers' Milk Bureau and the Directory for Mothers' Milk, Boston. Histories of the cases are recorded in tables 2 and 3. Samples were studied from 9 nursing mothers at the Detroit bureau and from 10 mothers at the Boston directory. The mother in case 1 was treated for five years for adolescent goiter, but at the time of the study showed no signs of thyroid complications. No past or present thyroid

TABLE 2.—*Histories of Detroit Mothers Who Supplied Milk*

Case	Race	Age, Years	Body Weight, Kg.	General Health	Number of Pregnancies	Birth of Infant	Date of Birth	Date of Study	Duration of Study, Weeks	Weight of Baby at Birth, Kg.	Weight of Baby Later, Kg.
1	W*	37	65.2	G†	5	P‡	10/28/31	2/ 1/32	22	1.3	3.6, 1/28/32
2	W	..	67.5	Ex	3	N	8/30/31	2/ 1/32	10	3.2	5.9, 12/ 2/31
3	W	29	59.1	G	1	N	9/ 7/31	2/ 1/32	19	3.2	5, 12/ 1/31
4	W	31	67.7	G	3	N	9/13/31	2/ 1/32	22	4.1	5.8, 12/10/31
5	W	33	73.8	G	2	N	1/19/32	2/ 1/32	22	3.2	5.4, 4/ 8/32
6	W	24	92.7	G	2	N	5/17/32	11/ 7/32	11	3.9	6.4, 9/ 6/32
7	W	29	61.2	G	1	N	9/12/32	11/ 7/32	13	3.6	6.1, 1/25/33
8	W	18	63.0	G	2	N	9/13/32	11/ 7/32	3	3.3	
9	W	22	60.3	G	1	N	12/21/32	1/24/33	2	3.1	4.1, 1/17/33

* W, white American.
† G, good; Ex, excellent.
‡ N, normal; P, premature, 7 months.

TABLE 3.—*Histories of Boston Mothers Who Supplied Milk*

Case	Race	Age, Years	Body Weight, Kg.	General Health	Number of Pregnancies	Birth of Infant	Date of Birth	Date of Study	Duration of Study, Weeks	Weight of Baby at Birth, Kg.	Weight of Baby Later, Kg.
1	I*	29	63.0	Ex†	2	N‡	12/14/31	3/ 2/32	33	3.0	6.3, 4/10/32
2	W	26	68.4	G	2	N	10/23/31	3/ 2/32	6	3.5	8.1, 3/15/32
3	W	24	69.7	Ex	3	C	1/ 1/32	3/ 2/32	33	2.9	5.4, 3/21/32
4	I	26	65.2	G	1	N	12/25/31	3/ 2/32	29	3.7	6.7, 4/26/32
5	I	22	67.5	G	3	N	3/27/32	4/13/32	44	3.5	4.3, 4/26/32
6	W	19	54.0	G	1	N	8/ 1/32	9/21/32	14	3.6	7.8, 11/ 2/32
7	W	24	62.5	G	4	N	9/21/32	10/19/32	5	3.6	3.8, 10/21/32
8	C	25	59.4	G	3	N	8/ 7/32	11/ 2/32	15	3.1	6.1, 11/ 4/32
9	W	23	54.0	G	6	N	6/21/32	11/23/32	12	3.9	6.4, 9/12/32
10	W	26	70.2	G	4	N	11/ 4/32	1/ 4/33	6	4.4	5.9, 1/ 4/33

* I, Italian; W, white American; C, colored.
† Ex, excellent; G, good.
‡ N, normal; C, cesarean.

complications were recorded for the remaining eighteen mothers. The mother in case 5 used iodized salt continually, and those in cases 6 and 7 used it occasionally. None of the women of the Boston directory reported the use of iodized salt. The women in this investigation with the exception of the mother in case 8 (social service) lived with their families and had adequately balanced diets.

Manner of Collecting Samples.—One ounce (28.34 cm.) of milk was received each week from each woman under observation. The samples from the Detroit bureau represented a portion of the total amount expressed manually from both breasts. The women were accustomed to this procedure, which occurred each day at about 10 a. m. The samples for analysis were collected on the same day each week. The samples received from the Boston directory were from pools of a

number of expressions representative of the mixed twenty-four hour milk from the same mother. Collections in Boston were made on the same day each week, and the samples were shipped in ice and were received at the laboratory on the following morning. All the mothers nursed their babies, and the samples were collected immediately after nursing. The mode of expression differed with the individual mother. In case 1 both manual expression and a breast pump were used; in cases 3, 6, 7 and 8, a water power breast pump; in cases 4, 2 and 5, a hand breast pump; in 9 and 10, manual expression. The mothers gradually became accustomed to their individual mode of expression. Entire emptying of the breasts was advised at each expression.

ANALYTIC METHODS

Microdeterminations were made of the calcium, phosphorus and iodine. This was necessary since samples of only 1 ounce were received and 10 cc. of this was needed for the micro-estimation of iodine. The iodine determinations were made on fat-free milk as described elsewhere,[12] with the exception that four times normal potassium hydroxide was used for alkalinization instead of four times normal potassium carbonate. Attempts to hydrolyze the whole milk by the method of Maurer and Diez [1] did not prove satisfactory. The analyses for calcium and inorganic soluble phosphates were made on the trichloracetic acid filtrates from skimmed milk, using Sander's method.[13] The presence of fat interfered with colorimetric measurement by causing a cloudiness. The calcium was estimated by the method which Clark [14] described for serum. The inorganic soluble phosphates were determined by the method of Benedict and Theis.[15]

Preparation of the Milk for Analysis.—Pour the sample of milk into a 20 cc. separatory funnel. Place the funnel in the icebox in an upright position and allow it to stand over night. The cream rises to the top. The following morning draw off the skimmed milk, and set aside 10 cc. to be used in the analysis for iodine content. Pipet 2 cc. of the fat-free milk into a test tube. Add 4 cc. of distilled water, followed by 4 cc. of 20 per cent trichloracetic acid. Cork the tube and shake well. Let the mixture stand for ten minutes and filter into a dry, clean test tube. The filtrate should be clear and colorless. If cloudiness is present refilter through the same filter paper. This filtrate is used for the determination of calcium and inorganic soluble phosphates.

Procedure for Iodine.—The procedure for the iodine determination is identical with that described for determining the iodine volume of the blood.[12] All possible sources of error were carefully watched.[16] The method involves combustion with oxygen in an open dish, removal of interfering substances, oxidation with bromine and comparison of the color produced with the starch-iodide reaction in a micro-colorimeter.

Procedure for Calcium.—Place 1 cc. of the trichloracetic acid filtrate in a small centrifuge tube. Add 1 drop of methyl orange indicator, then 50 per cent ammonium hydroxide drop by drop until the solution is alkaline. Add 1 cc. of 3 per

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13. Sanders, G. P.: J. Biol. Chem. **90**:747, 1931.
14. Clark, G. W.: J. Biol. Chem. **44**:487, 1921.
15. Benedict, S. R., and Theis, R. C.: J. Biol. Chem. **61**:63, 1924.
16. Turner, R. G., and Weeks, M. Z.: J. Am. Chem. Soc. **55**:254, 1933.

cent ammonium oxalate, mix slowly, and let stand for twenty-four hours to insure complete precipitation of the calcium oxalate. Rub down the walls of the centrifuge tube with a rubber policeman and centrifugate until clear. Decant the supernatant liquid, and add 10 cc. of distilled water. Stir up the precipitate in the tube, centrifugate, and decant the supernatant liquid as before. Add 5 cc. of normal sulphuric acid. Place the tube in a water bath at from 75 to 80 C. for ten minutes. Remove, and while hot titrate with hundredth-normal potassium permanganate. Standardize the permanganate against hundredth-normal oxalic acid. One cubic centimeter of hundredth-normal potassium permanganate is equivalent to 0.2 mg. of calcium.

Titration in cubic centimeters $\times$ 0.2 $\times \frac{100}{0.2}$ = milligram of calcium per hundred cubic centimeters.

Procedure for Inorganic Soluble Phosphates.—Place 3 cc. of the trichloracetic acid filtrate in a sugar tube. To a similar tube add 3 cc. of a standard phosphate solution containing 0.025 mg. of phosphorus. Dilute each with 5 cc. of water. Add to both tubes 1 cc. of Benedict's hydroquinone-bisulphite reagent and 1 cc. of his molybdic acid reagent. Stopper the tubes loosely and heat in a boiling water bath for ten minutes. Cool and compare in a colorimeter. The results are calculated in terms of phosphorus.

$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times 0.025 \times \frac{100}{0.6}$ = milligram of inorganic soluble phosphorus per hundred cubic centimeters of skimmed milk.

Comparison of Microdeterminations with Macrodeterminations.—A comparison was made of the microdeterminations and the standard macrodeterminations of calcium and phosphorus. The macrodeterminations were made on 24 mixed samples of whole milk from 4 women; the microdeterminations, on the skimmed milk of the same mixed samples. Ten cubic centimeters of whole milk was taken for each analysis. The sample was ashed in a nickel crucible and the ash was taken up with dilute hydrochloric acid (1:10). The total phosphorus was determined by the method reported in the second edition of "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists." The calcium was estimated by the method reported in the fourth edition of "Standard Methods of Chemical Analysis," by Scott.[17]

The average difference between the macrodeterminations of calcium in skimmed milk and the macrodeterminations on whole milk was $\pm$ 0.67 mg. This is in agreement with the results of Rothwell[18] and Sanders,[13] who found that the calcium of milk is practically all in the form of inorganic soluble calcium. The microdeterminations of inorganic soluble phosphorus on skimmed milk were from 32 to 40 per cent lower than the macrodeterminations of total phosphorus of the whole milk. Burhans and Smith,[19] in a study of the inorganic constituents of milk, reported the inorganic soluble phosphorus to be practically one third of the total phosphorus.

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17. Scott, W. W.: Standard Methods of Chemical Analysis, ed. 4, New York, D. Van Nostrand Company, Inc., 1925, vol. 1.

18. Rothwell, C. S.: J. Biol. Chem. **75**:23, 1927.

19. Burhans, C. W., and Smith, D. N.: The Inorganic Constituents of Human Milk with Particular Reference to Racial Variations, Am. J. Dis. Child. **26**:303 (Oct.) 1923.

RESULTS

The results presented represent the findings from the analysis of 295 samples of milk. At the beginning of the study many of the mothers were in the third to fifth month of lactation and most of those studied from the first month of lactation became short of their surplus before the end of the period of lactation. For this reason the results given in tables 5 to 9 represent the average amounts found from week to week during the time mentioned. The entire time of lactation is divided into four periods. The first period includes the first and second months of lactation, the second includes the third, fourth and fifth months, the third includes the sixth, seventh and eighth months and the fourth period the ninth, tenth and eleventh months. In tables 10 and 11 the average for each case is the mean of the weekly values during the first half and the last half of the period of lactation. The first half includes from the first to the fifth month and the last half, from the sixth to the eleventh month. In table 12 each figure represents the mean monthly value of all the cases. Table 13 gives the approximate amount of iodine a child would consume monthly. In this investigation there was only 1 subject who was followed through the entire mature period of lactation. Thus the results can be based only on averages. It is hoped that further investigation will make available a number of complete cases.

The typical weekly fluctuations encountered for calcium inorganic soluble phosphorus and iodine over a period of fourteen weeks are shown in table 4. The results were selected from 1 case from each locality. The weekly variations are typical of all the cases studied for any stage of the period of lactation. Only in the monthly averages are there noticeable changes. The magnitude of the weekly variations of the iodine content of the milk is greater for the Boston women than for the Detroit women. However, the average variations for the fourteen weeks are similar, 3 and 2.2 micrograms, respectively. The average fluctuations of the calcium and inorganic soluble phosphorus of the milk are greater for the Boston woman than for the woman in Detroit. For the Boston milk there is shown an average variation of calcium of 4 mg.; for the Detroit milk, 2.9 mg. The most marked difference is in the phosphorus findings, 1.9 and 0.5 mg., respectively. This greater weekly variation in the Boston milk may be due to the fact that the samples were one day older than the Detroit milk when analyzed.

Iodine.—The average iodine values for skimmed milk from the women of Boston and Detroit are presented in table 5. There is a marked variation in the individual cases, but this is not uncommon for other constituents of milk. During the third period of lactation there is a range of from 9.2 to 14.7 micrograms per hundred cubic centimeters

in the milk from Boston. A like range of from 8 to 16.1 micrograms is seen in the milk from Detroit for the same period. The largest difference between the two groups is seen during the first period of lactation. The Boston milk shows 8.3 micrograms against 14.3 micrograms for

TABLE 4.—*Weekly Fluctuations of the Iodine, Calcium and Inorganic Soluble Phosphorus in Human Skimmed Milk*

Iodine, Micrograms per 100 Cc.				Calcium, Mg. per 100 Cc.				Phosphorus, Mg. per 100 Cc.			
Boston*	V	Detroit†	V	Boston*	V	Detroit†	V	Boston*	V	Detroit†	V
7	....	14	....	36.9	.....	40.3	.....	5.2	.....	4.1	.....
6	— 1	13	— 1	37.5	+ 0.6	32.7	— 7.6	5.5	+0.3	4.7	+0.6
9	+ 3	14	+ 1	37.9	+ 0.4	37.2	+ 4.5	6.5	+1.0	4.9	+0.2
9	0	16	+ 2	41.8	+ 3.9	34.8	— 2.4	8.7	+2.2	4.1	—0.8
7	— 2	18	+ 2	37.7	— 4.1	39.1	+ 4.3	8.2	—0.5	5.0	+0.9
7	0	17	— 1	35.5	— 2.2	35.4	— 3.7	6.8	—1.4	4.8	—0.2
8	+ 1	15	+ 2	40.9	+ 5.4	38.0	+ 2.6	11.5	+4.7	4.4	—0.4
8	0	19	+ 4	46.7	+ 5.8	36.1	— 1.9	8.9	—2.6	4.3	—0.1
19	+11	16	— 3	49.2	+ 2.5	36.4	+ 0.3	13.2	+4.3	5.6	+1.3
7	—12	19	+ 3	35.8	— 3.4	31.0	— 5.4	10.1	+3.1	4.9	—0.7
9	+ 2	17	— 2	36.2	+ 0.4	32.9	+ 1.9	6.9	—3.2	4.0	—0.9
10	— 1	10	— 7	36.1	— 0.1	34.0	+ 1.1	8.1	+1.2	4.0	0.0
..	....	8	— 2	46.1	+10.0	33.1	— 0.9	9.3	+1.2	4.1	+0.1
13	+ 3	8	0	34.8	—11.3	32.8	— 0.3	8.2	—1.1	4.9	+0.8
7	— 6	9	+ 1	41.4	+ 6.6	27.9	— 4.9	8.7	+0.5	4.5	—0.4
Average	± 3.0		± 2.2		± 4.0		± 2.9		±1.9		±0.5

* The values are those found in case 5 in lactation weeks 4 to 18.
V, variation.
† The values are those found in case 4 in lactation weeks 21 to 35.

TABLE 5.—*Average Iodine Value of Human Skimmed Milk* *

Case	Number of Samples	Boston Lactation Months 1 to 2	3 to 5	6 to 8	9 to 11	Number of Samples	Detroit Lactation Months 1 to 2	3 to 5	6 to 8	9 to 11
1	31	....	10.9	10.9	9.1	22	....	14.1	10.1	....
2	6	....	14.6	14.3	....	11	....	....	15.8	....
3	30	....	10.6	11.6	7.5	19	....	14.0	12.8	10.0
4	27	....	11.5	9.7	8.6	22	....	13.3	13.9	9.9
5	37	7.3	10.0	9.2	13.2	21	23.0	19.9	8.0	....
6	13	10.0	10.8	....	....	9	....	....	16.1	....
7	5	7.7	....	....	....	11	9.0	15.1	....	....
8	12	...	11.4	14.7	....	3	9.0	12.0	....	....
9	9	...	....	13.2	....	2	15.0	....	....	....
10	5	...	13.8	....	....	0	....	....	....	....
Total	175					120				
Average		8.3	11.7	11.9	9.6		14.2	14.7	12.8	9.95

* Iodine in micrograms per hundred cubic centimeters. One microgram = 0.001 mg.

the Detroit milk. The highest iodine content is that in case 5 (Detroit), 23 micrograms. The mother used iodized salt daily, and her milk continually showed a high content of iodine up to the sixth month of lactation, when it dropped to 8 micrograms. The latter average consists of only 1 determination for that period. The mothers in cases 6 and 7 (Detroit) used iodized salt occasionally. This may account for the high value of iodine in the milk in case 6 during the third period. In the samples from Boston the average iodine content is seen to

reach its peak during the third period, 11.9 micrograms. This, however, is only slightly above that of the second period, 11.7 micrograms. Therefore, the average findings show a rise in the iodine content of the milk from the first and second months of lactation to the third and fifth, this level being then maintained to the eighth month, after which it drops during the month to 9.6 micrograms. The average iodine value of the Detroit samples reaches its peak in the second period, falling slightly during the third period, and approaching the value found for the Boston milk in the fourth period, 9.95 micrograms. With the exception of case 5 (Boston) the iodine values in each case decline toward the end of the period of lactation. Throughout the entire period of lactation the average values in all cases in the Detroit group remain above those found for the milk from the Boston mothers.

TABLE 6.—*Average Calcium Value of Human Skimmed Milk* *

Case	Number of Samples	Boston Lactation Months				Number of Samples	Detroit Lactation Months			
		1 to 2	3 to 5	6 to 8	9 to 11		1 to 2	3 to 5	6 to 8	9 to 11
1	33	....	37.1	37.0	35.8	22	....	38.4	35.4	....
2	6	....	37.1	38.6	....	12	....	....	34.1	....
3	33	....	33.6	32.2	31.4	21	....	30.9	30.3	28.3
4	29	....	38.9	35.6	34.5	24	....	33.6	34.5	33.5
5	42	37.3	39.6	40.4	39.7	24	41.3	36.2	36.2	....
6	14	33.1	33.0	....	....	9	....	....	32.7	....
7	5	39.6	....	....	....	11	44.2	45.5	....	....
8	13	....	43.7	40.3	....	3	38.7	44.2	....	....
9	10	....	....	38.5	....	2	42.8	....	....	....
10	6	....	40.7	....	....	0	....	....	....	....
Total	191					128				
Average		36.6	37.9	37.6	35.3		41.7	38.1	33.8	30.4

* Calcium in milligrams per hundred cubic centimeters.

Calcium.—The average calcium content in the milk from Boston mothers during the first period is 36.6 mg. per hundred cubic centimeters, with a slight increase to 37.9 during the third to fifth months of lactation gradually dropping to 35.3 mg. in the last period. Higher values are found for the calcium content of the milk of Detroit mothers during the first and second months of lactation. There is no rise during the second period, but a steady decline to 30.4 mg. in the last stages of lactation. Though in the early months the calcium of the Detroit mothers' milk is more concentrated than that of the Boston mothers' milk the decrease during the entire period of lactation is of greater magnitude.

Inorganic Soluble Phosphorus.—The average figures for the inorganic soluble phosphorus in human skimmed milk are recorded in table 7. The Boston samples have an average of 6.3 mg. per hundred cubic centimeters for the first and second periods of lactation, with a slight decrease to 5.8 mg. in the last stage. The figures for the Detroit samples are

highest during the first two months of lactation, falling gradually to 4.7 mg. in the last stage. The decline in the inorganic soluble phosphorus is not so rapid for the Boston group as for the Detroit group. This compares with the average decline in calcium during the entire period of lactation for each group. Individually the fluctuations differ. In case 1 (Boston) there is an increase of from 6.3 mg. in the second period of lactation to 7.1 in the last period. A similar finding is made in case 3 (Detroit). Telfer [20] pointed out that the phosphorus content of human milk varies according to the mode of living. He found that for women living in the country the figures are distinctly higher than for town dwellers. This may explain the increase during the later stages in the 2 cases mentioned. However, the majority of the cases and

TABLE 7.—*Average Inorganic Soluble Phosphorus Value of Human Skimmed Milk* *

Case	Number of Samples	Boston Lactation Months				Number of Samples	Detroit Lactation Months			
		1 to 2	3 to 5	6 to 8	9 to 11		1 to 2	3 to 5	6 to 8	9 to 11
1	33	...	6.3	6.5	7.1	23	...	4.6	5.2	...
2	6	...	7.3	5.7	...	12	...	...	7.6	...
3	33	...	4.3	4.1	3.8	21	...	4.8	4.8	5.1
4	29	...	5.1	5.1	4.3	24	...	4.1	4.5	4.3
5	41	6.3	9.0	10.3	8.0	24	6.3	6.7	6.9	...
6	14	6.0	5.8	...	...	9	...	...	3.9	...
7	5	6.8	...	...	...	9	7.1	6.8	...	...
8	12	...	6.6	6.3	...	3	8.5	8.4	...	...
9	10	...	...	5.5	...	0	...	...	...	...
10	5	...	6.1	...	...	0	...	...	...	...
Total	188					125				
Average		6.3	6.3	6.2	5.8		7.3	5.9	5.5	4.7

* Inorganic soluble phosphorus in milligrams per hundred cubic centimeters.

the total average show an inverse relationship between the percentage of inorganic soluble phosphorus in human skimmed milk and the duration of the mature period of lactation. This is in agreement with the results of most investigations [21] of fluctuations in the total phosphorus of mother's milk during the entire period of lactation.

Ratio of Calcium to Iodine.—The fluctuation in the ratio of calcium to iodine (table 8) for individual cases in each group is considerable, the quotient varying from 2.08 to 5.14. The averages, however, show practically the same trend—a high quotient for the first two months of lactation, with a drop in the second and third periods, and finally a rise approaching that recorded for the first period. The Boston calcium-iodine quotient is greater throughout the entire period of lactation than

20. Telfer, S. V.: Biochem. J. **18**:309, 1924.

21. Nims, B.; Macy, I. G.; Hunscher, H. A., and Brown, M.: Human Milk Studies, Am. J. Dis. Child. **43**:1062 (May) 1932. Widdows, Lowenfeld and Taylor.[10] Telfer.[9]

the Detroit. This signifies that in the milk of Boston mothers the iodine is lower in relation to the calcium. The calcium-iodine quotient is approximately 20 per cent greater for the Boston than for the Detroit milk. The concentration of calcium in the Boston milk may range from 29,400 to 51,400 times as high as the iodine content. In the Detroit group the range is from 20,800 to 49,100. This shows the small amount of iodine present in contrast to the other constituents of milk. The fact that the ratio is not consistent aids in the belief that the mechanism by which the iodine is delivered into the milk is not the same as for calcium. Gaines [22] suggested that a constant ratio between two constituents in the milk perhaps indicates a close association in the mechanism of their secretion.

TABLE 8.—*Ratio of Calcium to Iodine in Human Skimmed Milk* *

	Boston Lactation Months				Detroit Lactation Months			
Case	1 to 2	3 to 5	6 to 8	9 to 11	1 to 2	3 to 5	6 to 8	9 to 11
1	....	3.40	3.39	3.93	....	2.72	3.50	....
2	....	2.54	2.69	....	....	....	2.15	....
3	....	3.16	2.86	4.18	....	2.20	2.36	2.83
4	....	3.38	3.67	4.01	....	2.52	2.48	3.38
5	5.10	3.96	4.39	3.00	1.79	1.81	4.52	....
6	3.31	3.05	....	....	....	....	2.08	....
7	5.14	....	....	....	4.91	3.01	....	....
8	....	3.83	2.74	....	4.30	3.68	....	....
9	....	....	2.91	....	2.85	....	....	....
10	....	2.94	....	....	....	....	....	....
Average	4.51	3.03	3.23	3.78	3.46	2.65	2.84	3.10

* Calcium-iodine quotient in terms of 1×10^{-3}.

Ratio of Calcium to Inorganic Soluble Phosphorus.—The ratio of calcium to inorganic soluble phosphorus remains fairly constant for each group (table 9). In both groups slight increase in the quotient appeared after the first two months of lactation, which continued through the later stages; that is, from 5.75 for the Boston mothers and 5.77 for the Detroit mothers to 6.57 and 6.66, respectively. Although the decline in both the calcium and the inorganic soluble phosphate during the eleven months is greater in the Detroit group than in the Boston group the ratios appear to be practically the same. The variations in the calcium-phosphorus quotient between individual cases is from 3.92 to as high as 8.26 for the Boston milk and from 4.48 to 8.38 for the Detroit milk. Considering that the total of the inorganic soluble phosphorus is approximately one third of the total phosphorus content of human milk, these quotients divided by 3 give approximately the calcium-phosphorus quotent found by other investigators to be most suitable for a nonrickets-producing milk. Widdows and her co-workers [10]

22. Gaines, W. L.: J. Dairy Sc. **8**:486, 1925.

reported the variations in the calcium-phosphorus quotient to be greater between individual mothers than the average quotient (which they gave as 2.17) over the whole course of lactation. Nims and her collaborators,[21] in a study of the chemical analysis of the components of milk found the calcium-phosphorus quotient for mother's milk to vary between 1.98 and 2.99. Other investigators [23] have found that diets in which the ratio of calcium to phosphorus varies within the limits of 1 : 2 are most suitable. The babies of all the mothers contributing to this study were reported as being healthy. Therefore, a calcium-inorganic soluble phosphorus quotient of not less than 5.75 or greater than 6.66 (our results for the entire lactation period) is probably the ratio most suitable for the child. Our method for the determination of these two

TABLE 9.—*Ratio of Calcium to Inorganic Soluble Phosphorus in Human Skimmed Milk* *

	Boston Lactation Months				Detroit Lactation Months			
Case	1 to 2	3 to 5	6 to 8	9 to 11	1 to 2	3 to 5	6 to 8	9 to 11
1	....	5.88	5.38	5.04	....	8.34	6.80	....
2	....	3.08	6.77	....	....	....	4.48	....
3	....	7.81	8.09	8.26	....	6.43	6.31	5.54
4	....	7.62	6.98	8.02	....	8.19	7.66	7.79
5	5.92	4.40	3.92	4.96	6.55	5.10	5.24	....
6	5.51	5.68	....	....	....	....	8.38	....
7	5.82	....	....	....	6.22	6.69	....	....
8	....	6.62	6.39	....	4.55	5.26	....	....
9	....	....	7.00	....	....	....	....	....
10	....	6.67	....	....	....	....	....	....
Average	5.75	6.22	6.36	6.57	5.77	6.67	6.48	6.66
Aver. Ca/P	1.91	2.07	2.12	2.19	1.92	2.22	2.16	2.22

* The calcium-phosphorus quotient calculated on the bases of one third is the calcium-inorganic phosphorus quotient.

constituents may, by reason of its rapidity and ease, and the small quantity of milk necessary, be of value in testing mother's milk for antirachitic properties.

Averages in First and Last Halves of Lactation Period.—Tables 10 and 11 present the average values for the calcium, the inorganic soluble phosphorus and the iodine in each case studied, as found in the first and last halves of the period of lactation. The iodine values for the Detroit group are slightly higher in the first half (first to fifth months, inclusive) than in the last half (sixth to eleventh months, inclusive) of the nursing period, with averages for all the cases of 14.5 and 12.4 micrograms, respectively. The calcium and inorganic phosphorus values are likewise higher during the first half of the course of lactation. For the Boston group the variations of these constituents between

23. Boss, Medes, McCollum and Osborne and Mendell, cited by Widdows, Lowenfeld and Taylor.[10]

the first and last halves of the period of lactation are not so great. The calcium shows a decrease of 0.6 mg. and the phosphorus, a decrease of 0.1 mg., while the iodine gains 0.7 micrograms in the last half. Therefore, the average iodine content for the first half of the period remains practically the same during the second half. In the goitrous

TABLE 10 *(Detroit Mothers).—Average Values of Iodine, Calcium and Inorganic Soluble Phosphorus in Skimmed Milk in the First and Last Halves of the Lactation Period*

		First Half				Last Half		
Case	Months	Calcium*	Phosphorus	Iodine†	Months	Calcium	Phosphorus	Iodine
1	4-5	38.4	4.6	14.1	6- 8	35.4	5.2	10.1
2	5	....	...	....	6- 8	34.1	7.6	15.8
3	5	30.9	4.8	14.0	6- 9	29.8	4.8	12.1
4	5	33.6	4.1	13.3	6-10	34.1	4.4	12.3
5	1-5	38.3	6.5	21.1	6	36.2	6.9	8.0
6	...	....	...	....	6- 8	32.7	3.9	16.1
7	2-5	45.2	6.9	13.5	....	....	...	....
8	2-3	41.4	8.4	10.5	....	....	...	....
9	2	42.8	...	15.0	....	....	...	....
Average.....		38.7	5.88	14.5		33.7	5.4	12.4

* Calcium and phosphorus in milligrams per hundred cubic centimeters of milk.
† Iodine in micrograms per hundred cubic centimeters of milk.

TABLE 11 *(Boston Mothers).—Average Values of Iodine, Calcium and Inorganic Soluble Phosphorus in Skimmed Milk in the First and Last Halves of the Period of Lactation*

		First Half				Last Half		
Case	Months	Calcium*	Phosphorus	Iodine†	Months	Calcium	Phosphorus	Iodine
1	3-5	37.1	6.3	10.9	6-11	36.5	6.8	10.0
2	5	37.1	7.3	14.6	6	38.6	5.7	14.3
3	3-5	33.6	4.3	10.6	6-10	32.5	4.0	9.7
4	3-5	38.9	5.1	11.5	6- 9	35.3	4.9	9.4
5	1-5	38.7	7.8	8.9	6-11	40.1	9.1	11.2
6	2-5	33.0	5.8	10.4	....	....	...	....
7	1-2	39.6	6.8	7.7	....	....	...	....
8	3-5	43.7	6.8	11.4	6- 7	40.3	6.3	14.7
9	...	....	...	....	6- 8	38.5	5.6	13.2
10	3-4	40.7	6.0	13.8	....	....	...	....
Average.....		38.0	6.2	11.1		37.4	6.1	11.8

* Calcium and phosphorus in milligrams per hundred cubic centimeters of milk.
† Iodine in micrograms per hundred cubic centimeters of milk.

region there was a fall of 2.1 micrograms; in the nongoitrous region, a rise of 0.7 micrograms. The gradual declines in the three constituents are not brought out so clearly when the time of lactation is divided into halves as when (tables 5, 6 and 7) it is considered in four periods.

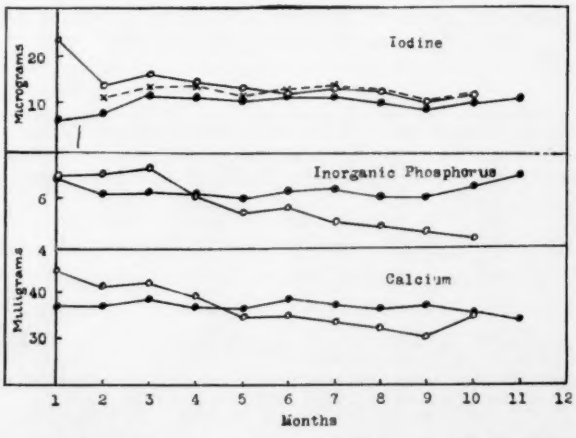
Monthly Averages.—The monthly averages of all the cases show the fluctuations of the three constituents more plainly, and possibly give a truer idea of the trend during the period of lactation. These figures are given in table 12, and the curves plotted therefrom are shown in the chart.

Comparison of the findings for the goitrous with those for the nongoitrous region shows a higher iodine value for the Detroit group than for the Boston group, with an average percentage difference of

TABLE 12.—*Average Monthly Values of Iodine, Calcium and Inorganic Soluble Phosphorus in Human Skimmed Milk in All Cases*

	Iodine, Micrograms per 100 Cc.					Calcium, Mg. per 100 Cc.					Phosphorus, Mg. per 100 Cc.				
Month of Lactation	Detroit*	Number of Cases	Boston†	Number of Cases	Percentage Difference	Detroit	Number of Cases	Boston	Number of Cases	Percentage Difference	Detroit	Number of Cases	Boston	Number of Cases	Percentage Difference
1	23.0	1	7.0	2	+69.5	44.0	2	37.5	2	+14.7	6.9	1	6.5	2	+ 5.7
2	14.0	4	8.7	3	+37.8	41.0	4	37.3	3	+ 9.2	7.1	3	6.3	3	+11.2
3	17.4	3	12.0	7	+31.0	42.8	3	39.1	7	+ 8.6	7.1	3	6.4	7	+ 9.8
4	15.7	3	11.2	6	+28.6	39.5	3	38.5	7	+ 2.5	6.1	3	6.2	7	— 1.6
5	14.7	5	10.7	7	+27.2	35.2	5	36.2	7	— 2.8	5.4	5	6.0	7	—11.1
6	12.7	6	11.3	7	+11.0	35.2	6	38.8	7	—10.2	5.6	6	6.3	7	—12.5
7	15.6	5	11.6	5	+25.6	33.5	5	37.3	6	—11.3	5.3	5	6.3	6	—18.8
8	11.9	5	11.0	5	+ 7.5	31.3	5	35.8	5	—14.3	5.0	5	6.0	5	—20.0
9	9.7	2	9.4	4	+ 3.0	29.8	2	36.2	4	—21.4	4.8	2	6.0	4	—27.0
10	10.3	1	10.0	3	+ 2.9	35.7	1	35.4	3	+ 0.8	4.0	1	6.5	3	—62.5
11	....	..	11.5	2	.....	....	..	36.7	2	.....	...	..	7.0	2	.....
Aver. percentage difference					+24.1					± 9.5					±18.0

* Goitrous region.
† Nongoitrous region.



Average monthly values of iodine, inorganic phosphorus and calcium in mother's milk in all cases of each group. The unbroken line with open circle indicates the values for the Detroit group; the broken line, the values for the Detroit group without case 5, and the unbroken line with solid circles, the values for the Boston group.

plus 24.1. This percentage difference is greatest, 69.5, during the first month of lactation, descending gradually to 11 in the sixth month, then rising in the seventh to 25.6, after which it falls rapidly to 2.9 in the tenth month. Comparison of the averages of the calcium and inorganic

soluble phosphorus values shows that the fluctuations from month to month vary from plus to minus, and that there is no continual increase or decrease of these constituents for either group. The percentage difference is more marked for the inorganic soluble phosphorus values, averaging 18, than for the calcium, averaging 9.5. Considering the special adaptability of the human organism it is not surprising that such variations should be found between two distinct groups of persons.

On plotting the figures the iodine values for the Detroit group are found to descend near the values for the Boston group in the later months of lactation. Omitting case 5 (Detroit), in which iodized salt was used continually, the iodine curve closely resembles that of the Boston group, although the average value continually remains at a higher level. The calcium and inorganic soluble phosphorus curves are parallel. The milk from the Detroit mothers has greater concentrations of both these constituents during the early months of lactation. The values drop continually until the fourth month, when they reach approximately the same level as do those found for the Boston group, and then gradually fall below this level. This indicates that there is a greater decrease in both calcium and phosphorus content in the milk of Detroit mothers during the later stages of lactation than in the milk of Boston mothers. McCollum and his co-workers [24] emphasized the fact that the ratio of calcium to phosphorus in the diet is more important than the absolute amounts of the salts themselves. They showed that a deficiency of phosphorus in the diet gives rise to rickets only when the calcium is present in an amount that gives a ratio of calcium to phosphorus considerably above the normal 1:2. Sherman and his associates [25] believed that when the deficiency of either element is too great, a retardation of the deposition of calcium phosphate in the bone cannot be counterbalanced by increasing the antirachitic vitamin in the diet. Both constituents in the milk of Detroit mothers fall below the level of the corresponding elements in the milk of Boston mothers, but the ratio of calcium to phosphorus remains normal. Vitamins restore the balance between calcium and phosphorus. Therefore the milk of Detroit mothers giving rise to rickets can best be corrected by feeding the mothers some form of calcium and phosphorus.

The average amount of iodine consumed each month by the infant has been computed from the average amount of iodine found in 100 cc. of milk each month and the approximate amount of milk consumed each

24. McCollum, E. V.; Simmonds, N.; Shipley, P. G., and Park, E. A.: J. Biol. Chem. **47**:50, 1921.

25. Sherman, H. C., and Quinn, E. J.: J. Biol. Chem. **67**:667, 1926. Sherman, H. C., and Pappenheimer, A.: Proc. Soc. Exper. Biol. & Med. **18**:193, 1921. Sherman, H. C., and Macleod, F. L.: J. Biol. Chem. **64**:429, 1925.

month. The average amount of milk consumed daily as reported by Findlay [26] ranges gradually from 16 ounces (497 Gm.) the first week to 30 ounces (933 Gm.) at the twentieth week, at which time the quantity reaches 35 ounces (1,089 Gm.) a day during the remaining weeks of lactation. The calculations for the average consumption of iodine from human milk for goitrous and nongoitrous regions are given in table 13. The average amount consumed per month for the entire period of lactation is 3.23 mg. for the Detroit infants as compared with 2.48 for the Boston infants. The amount of iodine consumed by the infant of a Detroit mother during the first month of lactation is nearly 4 times the amount of iodine consumed by the infant of a Boston mother. The average amount of iodine found in the first month of lactation of Detroit women is 23 micrograms, and represents the weekly average of only

TABLE 13.—*Child's Approximate Monthly Iodine Consumption Based on the Average Monthly Iodine Value of Human Milk in All Cases*

Month of Lactation	Quantity of Milk Consumed Monthly, Cc.	Iodine Value of Milk, Mg. per 100 Cc.		Quantity of Iodine, Consumed Monthly, Mg.	
		Detroit	Boston	Detroit	Boston
1	13,749	0.0230	0.0070	3.16	0.96
2	18,730	0.0140	0.0087	2.62	1.62
3	21,153	0.0174	0.0120	3.68	2.53
4	21,826	0.0157	0.0112	3.42	2.44
5	22,500	0.0147	0.0107	3.30	2.40
6	26,924	0.0127	0.0113	3.41	3.04
7	26,924	0.0156	0.0116	4.20	3.12
8	26,924	0.0119	0.0110	3.20	2.96
9	26,924	0.0097	0.0094	2.61	2.52
10	26,924	0.0103	0.0100	2.77	2.69
11	26,924	.....	0.0115	....	3.09
Average iodine value		0.0145	0.0104		
Average consumption				3.23	2.48

1 case (5), the mother in this case being accustomed to use iodized salt. Therefore, the finding cannot be emphasized. However, omitting case 5 in the average for the Detroit women, the average iodine content beginning with the second month still remains higher than that found for the Boston milk (chart). The average daily consumption therefore remains greater. The quantity of iodine consumed monthly does not vary greatly from the mean throughout the entire period. This is found true for both groups studied, yet the volume of milk consumed monthly increases steadily to the sixth month. The slight increase noted in both groups after the ninth month is not uncommon for the other constituents in milk. Nims [21] and co-workers found a decrease in the phosphorus of human milk during the mature period (from first to ninth months), after which this constituent regained a high level at the fourteenth month. In general the results show that the iodine content

26. Findlay, L.: Practitioner **125**:5, 1930.

of human milk follows the trend of the calcium and the phosphorus content decreasing in concentration after the third month to the end of the mature period.

COMMENT

Although the milk secreted by different women has been shown to vary in composition from time to time, even from day to day, or during a single nursing period, the general findings in this study show that the calcium and phosphorus concentrations in human milk tend to decrease during the period of lactation after the third or fourth month. Since these results confirm the findings of other investigators they will not be discussed further.

The average iodine content of human skimmed milk reported in this study varied between different women and at different times during the period of lactation from 6 to 23 micrograms, averaging 12.4. These findings are higher than those of foreign investigators for cow's milk (from 1 to 3 micrograms) and for human colostrum and mother's milk after the fourth or fifth days of lactation (from 2 to 4 micrograms). Calculating on the basis of the liquids, workers in this country have found the iodine content of skimmed cow's milk to lie between 1.8 and 16.9 micrograms. Since a detailed study of the iodine content of human milk during the entire period of lactation has not previously been made it seems justifiable to contribute these results.

The average iodine content of human skimmed milk determined from the milk of 9 women living in a goitrous region is higher throughout the period of lactation than that of milk from 10 mothers in a nongoitrous region, averaging 14.5 and 12.4, respectively. The percentage difference is greatest in the early months. After the eighth month the difference between the findings in the two localities diminishes, with a percentage difference of only 2.9 in the tenth month.

These findings represent a compensatory action on the part of the physiologic mechanism of the mother living in the goitrous section to supply a greater amount of iodine to the child than is naturally supplied in the milk of mothers in a nongoitrous region. It was anticipated that a lower concentration of iodine would be found in the milk of Detroit mothers. Hercus and Roberts [7] found a lower iodine content in the milk of goitrous women. In this study none of the subjects had goiter. As soon as an infant is born it becomes entirely dependent on the mother's milk for its iodine supply. Courth,[27] in a study of the passage of iodine from the sow to the fetus and the new-born pig, claimed that the sow delivers the greater part of her iodine to the colostrum. He also claims that the small amount of iodine in the thyroid gland of the fetus is not attributable to the activity of that gland.

27. Courth, H.: Landw. Jahrb. **69**:565, 1929.

Else,[28] in a report on congenital goiter, stated that if the thyroid gland of a mother is not secreting enough thyroxin during pregnancy a demand is thrown on the child's gland to function in utero. As a result there is a secretion of colloid which results in a colloid goiter. Why cannot this same demand be made on the infant's gland if, during the period of lactation, enough iodine is not supplied from the mother's milk? Goiter will not develop in the normal thyroid gland receiving a sufficient amount of iodine. Thus the theory of the compensating act of the mother to provide more iodine for an infant born in a goitrous region is reasonable as well as justified by the findings in this research. It shows further that the natural prevention of goiter in a person born with a normal thyroid gland in a goitrous region is the provision of an increased amount of iodine in the diet. Does the maternal physiologic mechanism provide for changing the iodine concentration of the milk to a higher one in a goitrous region? Bokelmann and Sheringer[29] found that the iodine content of the blood is relatively high in the second and third months of pregnancy, that it increases rapidly until the seventh month, remains at the same height until the ninth month, falls slightly in the ninth month, and declines very gradually after delivery, not reaching the normal level for some weeks. Grower and Tobey[30] observed that all changes in the composition of milk during starvation are directly related to simultaneous changes in the blood, and they claimed that in the production of milk a balance exists between the osmotic pressure of the milk and the blood. A study of the iodine of the blood in conjunction with the iodine of the milk during the period of lactation would be of interest.

Hercus and Roberts[7] found 8 micrograms of iodine per hundred cubic centimeters in the milk from a nongoitrous woman immediately after parturition. This content dropped to 1.6 in the fourth and fifth months of lactation. From these results he believed that the increase in the production of milk is not sufficiently great to compensate for the falling off in the iodine content.

The figures computed in this study show that in both goitrous and nongoitrous regions the increase in the output of the milk and the fall in the iodine concentration are sufficiently parallel to keep the amount of iodine consumed nearly constant.

It is an indisputable fact that a deficiency of iodine is a cause of goiter. This relationship is seen in the Great Lakes basin and on the Pacific coast where the surface water and hence the vegetation is defi-

28. Else, J. E.: Bull. A. Study Intern. Secret. **13**:40, 1929.
29. Bokelmann, A., and Sheringer, W.: Arch. f. Gynäk. **143**:512, 1931.
30. Grower, J. W., and Tobey, E. R.: J. Gen. Physiol. **15**:45, 1913.

cient in iodine. Mendel and Vickery [31] found in experimentation on rats that prolonged administration of iodine in doses of approximately 3.3 mg. per kilogram of body weight each day is apparently harmless. The efficient thyroid gland is able to utilize iodine and to produce the necessary amount of thyroxin even when the added load of pregnancy is thrown on it. Therefore the higher concentration of iodine found in the milk of mothers in a goitrous region is believed to be due to a compensatory act on the part of the mother's thyroid gland.

SUMMARY

1. The concentrations of three constituents of human milk—iodine, calcium and inorganic soluble phosphorus—are reported as found in chemical analyses of the milk of 9 mothers in a goitrous region and 10 mothers in a nongoitrous region during the mature period of lactation.

2. Microchemical methods are described for determining the amount of calcium and inorganic soluble phosphorus in 2 cc. of human skimmed milk.

3. The calcium and inorganic soluble phosphorus decrease after the third or fourth month of the period of lactation. The concentrations of these two constituents run parallel in each group. Both elements are more concentrated in the milk of mothers in Detroit in the early months of lactation, but fall below the values found for mothers in Boston after the fourth month.

4. The average iodine content of human skimmed milk may vary from 6 to 23 micrograms per hundred cubic centimeters, averaging 12.4 micrograms.

5. The average iodine content is greater throughout the period of lactation in goitrous regions than in nongoitrous regions. The percentage of difference is most marked during the early months of lactation.

6. After the third month of lactation the iodine shows a decline similar to that in calcium and phosphorus.

7. The calcium content is approximately 37,000 times as concentrated as the iodine content, varying between individual subjects and at different times during the period of lactation.

8. In both goitrous and nongoitrous regions the increase in the output of milk and the fall in the iodine concentration during the course of lactation are such as to keep the iodine consumed by the nursing infant practically constant.

9. The higher concentration of iodine in the milk of mothers in a goitrous region is believed to be due to compensatory activity on the part of the mother's thyroid gland.

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31. Mendel, L. B., and Vickery, H. B.: Proc. Soc. Exper. Biol. & Med. **27**: 806, 1930.

DENTAL DECAY AS AN INDICATOR OF A DIETARY FAULT

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HONOLULU, H. I.

During the last four years we have observed the effect of unusually one-sided diets on human teeth as well as on growth and general health. A series of articles have been written on our findings, especially in regard to a peculiar form of dental decay called odontoclasia, which affects the deciduous teeth. That this condition or any type of dental decay is caused entirely or partially by diet has long been a matter of contention. Soft food has been regarded as a cause by some, and sugar, heredity, lack of calcium or disturbance of the calcium-phosphorus ratio and deficiency in various vitamins, especially in vitamins C and D, by others. Mothers have usually accepted the decay of deciduous teeth as nature's way of getting rid of the weak milk teeth. In a previous paper [1] attention was called to the excellent teeth of the ancient Hawaiians. The teeth of 22 Polynesian children still living largely on the old native foods were examined and found to be almost perfect (the percentage of excellent teeth was 95.41). The teeth of another group of 55 Hawaiian children living in Honolulu and eating Oriental foods (mainly rice) were examined, and it was found that 98.2 per cent had decayed teeth. A recent [2] report from the Island of Triston de Cunha, 1,000 miles west of the Cape of Good Hope, apparently gives a striking confirmation of many of our observations. On this isolated island the teeth of 156 islanders (white) ranging in age from infancy to 92 years were examined, and 131 were found entirely free from decay. They never brush their teeth, and their food is soft. Their diet is described as follows: "They live on potatoes eaten without salt and unaccompanied by tea or other

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From the Research Department of the Queen's Hospital.

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1. Jones, Larsen and Pritchard: Dental Disease in Hawaii, Dental Cosmos **72**:439 (May); 574 (June); 685 (July); 797 (Aug.) 1930.

2. Bee, A. G.: Summary of an article in the Journal of the Royal Navy Medical Service, Dental Cosmos **74**:1031 (Oct.) 1932.

food. They eat fish with nothing else, and penguin eggs (also milk)." It is stated that "they eat a large quantity of potatoes." [2a]

The observations on the Hawaiians, added to the observations on Oriental children, and the added confirmation from the Island of Triston de Cunha seem to answer several questions: 1. Heredity is not the important factor in dental decay. 2. Soft foods with great "stickability" do not cause the decay; i. e., Hawaiian poi is softer than Oriental rice. 3. Sufficient calcium alone does not correct the fault; i. e., infants on mother's milk and children on cow's milk show decay. 4. Vitamin D alone does not correct the condition; a great deal of sunshine (seven and a half hours a day) as well as the addition of cod liver oil failed to prevent or arrest excessive decay. 5. Dental decay is due to a metabolic or dietary fault and not to an oral condition, since the beginning of the decay could be shown before the eruption of the teeth in children carried by rice-eating mothers.

That aciduric bacteria grow more readily in an acid mouth medium enhanced by an acid residue diet and that such bacterial action increases the rapidity of decay are granted. But a metabolic imbalance makes the environment favorable and alone can produce soft, chalky enamel, and it may produce a process of decay without any bacterial action.

Since these data were reported, observations have continued on the Ewa Plantation, and we now have a group of infants who have been carefully fed for from twelve to fifteen months on what we consider a balanced diet for a warm climate. During this same period other infants on the same plantation and of the same nationality were fed the usual Oriental diet. The children in group 1 were fed milk from rice-eating mothers,[3] supplemented with rice. Those in group 2 were fed cow's milk and rice.[4] Both groups received a small amount of vegetables and some eggs. In group 3 the rice was replaced by poi and potatoes (alkaline starches), and a little more vegetable than in diets 1 and 2 was added. The vitamin content of these three diets was sufficient to prevent any symptoms of deficiency. The calcium-phosphorus content of diets 2 and 3 was in excess of amounts considered optimal.

2a. A second confirmation has just appeared (Ferguson, J.: Am. Dent. A. **21**: 534 [March] 1934), giving tables showing that Samoan children eating taro and bananas (alkaline starches) showed only 0.84 per cent of carious teeth. The author speaks of miscegenation as a cause, but the Oriental children of Hawaii were largely of pure racial stocks and those on Tristan da Cunha were all "miscegenetic."

3. Two mothers were given a diet consisting exclusively of oats and raw food, including large amounts of raw peanuts.

4. The Orientals usually begin feeding rice at 6 months of age.

One outstanding difference in the diets was the difference in the acid-base balance. Diet 1 was neutral; diet 2 showed from 6 to 10 cc. excess alkali, and diet 3 showed an excess of alkali amounting to from 40 to 45 cc. With the increased metabolism which infants and children show, as compared to adults, they necessarily require more alkali in their food to maintain the same fluid balance. Such a dietary imbalance, therefore, if harmful, would affect infants more than adults. The urine of the infants on diets 1 and 2 (about 300 specimens were tested)

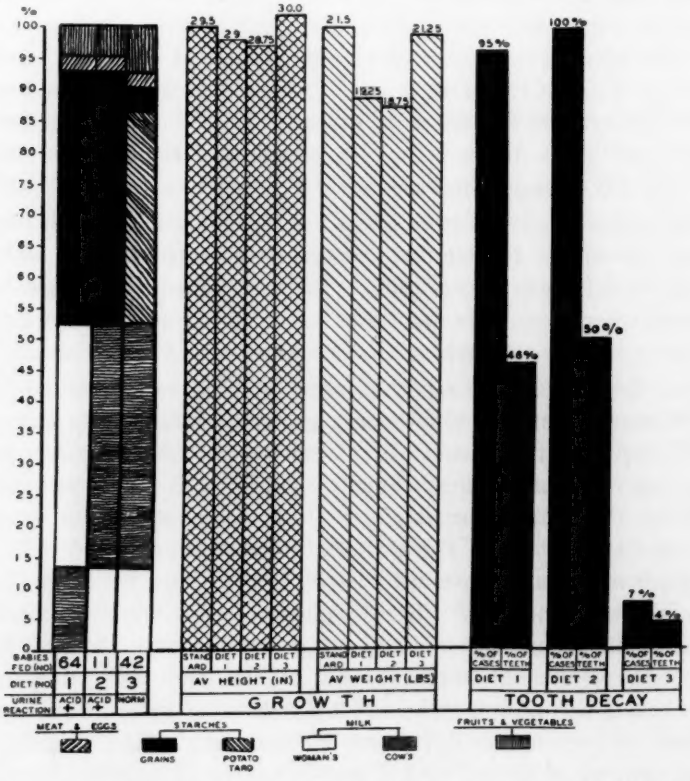

Fig. 1.—Comparisons of three diets in relation to curves for height and weight and to dental decay.

showed a p_H of 6 or less. The urine of infants on diet 3 (about 50 specimens were tested) usually showed a p_H of 6.5 or more. Frequently in these rice-eating babies of rice-eating mothers the metabolism is so upset that even a highly alkaline diet fails to change the reaction of the urine until the children have been constantly on the changed diet for many weeks.

Whether the condition of the acid-base balance in itself is sufficient to account for the differences noted, or whether it makes necessary food

substances more easily assimilable we do not know. The striking differences in the well-being and dental condition of the infants cannot be questioned.

In chart 1, columns 1 to 3 show the percentage of different foods taken by the different groups of infants. Columns 4 to 11 indicate the height and weight of these groups in relation to the standard for the white child. It will be noted that the infants on diet 3 are 1 inch

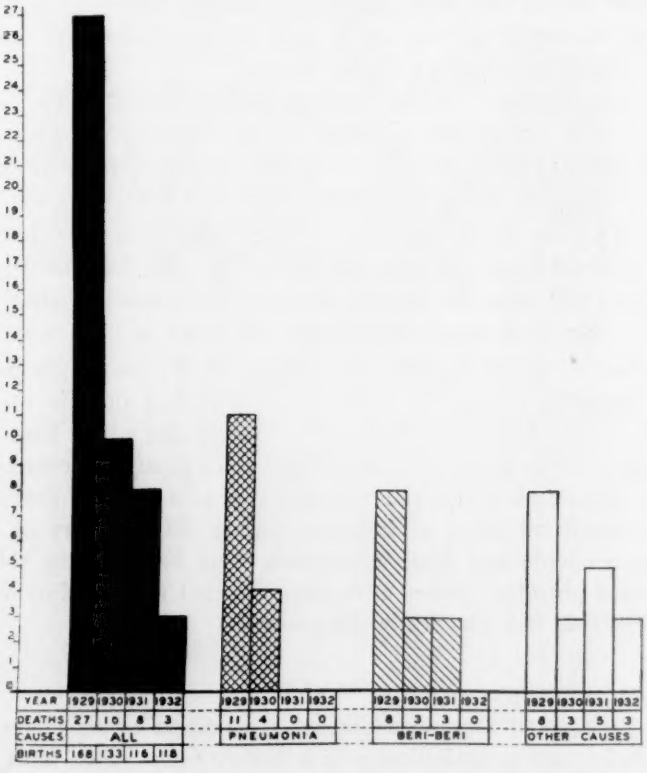

Fig. 2.—Infant mortality and principal causes of death on the Ewa Plantation from 1929 to 1932.

(2.54 cm.) taller and weigh 2 pounds (907.2 Gm.) more than the infants on diets 1 and 2. It is also interesting to note that these infants, who were once considered racially smaller than Anglo-Saxon children, are ½ inch (1.27 cm.) taller and weigh only 4 ounces (113.4 Gm.) less than the standard average for the white child.

The most dramatic change, however, is in the teeth. It will be noted that 95 per cent of the infants on diet 1 showed some dental decay and that 46 per cent of their teeth were decayed (576 erupted and 265 decayed). One hundred per cent of the infants on diet 2 showed decay,

and 50 per cent of the teeth were decayed (98 teeth erupted and 49 decayed). When these results are compared with the fact that only 7 per cent (3 out of 42) of the children on diet 3 and only 4 per cent (15 of 374) of the teeth showed decay, the difference seems more than a coincidence.

Concerning the effect of the educational work being done in connection with these studies on the children of the whole plantation, chart 2 gives some results that seem significant. These figures include all the residents, whether they cooperated, came to the clinics, were syphilitic or had a dozen children in as many years.

The program was one of feeding and of stressing the need of replacing much of the rice by other foods. Among the kindergarten children 101 paid 75 cents a month for an extra daily meal of poi, fruit and milk. Among the school children 550 of 1,035 ate an extra daily serving of poi for which they paid 1 cent. One of us (Dr. Jones) not only supervised these feedings personally, but also had meetings with the mothers and with the younger women. That some of these efforts bore fruit, even in the most antagonistic, there can be little doubt.

In chart 2, the first group of columns shows the infant mortality on the plantation during the four years. This is a drop in the infant death rate from 160.65 to 25.41. The drop in the whole Ewa district was from 111.9 to 85.3. The second and third groups of columns indicate that pneumonia and beriberi disappeared as a cause of death. This is more significant when we consider that in the Territory of Hawaii bronchopneumonia and lobar pneumonia were listed as the third and fourth most prevalent causes of death. Beriberi was listed as the fifth. Infant diarrhea has practically disappeared.

COMMENT

We have noted that odontoclasia, a condition of excessive dental decay can be used as an indicator of a dietary fault. This fault is associated with a high infant mortality and morbidity. An attempt at corrective feeding has shown that the condition practically disappears following a change of diet. When such a diet is instituted the curve for height and weight of Oriental babies comes up to the standard curve for height and weight of northern European children. The observations also suggest that the diet which will correct the dental defect will also raise the resistance to certain diseases. These diseases are some of the most prevalent causes of the high infant mortality in the Hawaiian Islands, i. e., berberi, diarrhea and pneumonia. It is hoped that the observations on the present group of infants may continue throughout childhood.

The observations suggest that in countries with warm climates where an acid residue diet high in carbohydrate is prevalent, the exchange of the acid starch for an alkaline starch and the addition of a small amount of vegetables will alter dental structure and general growth as well as affect infant morbidity and mortality. It may suggest that some of the concepts of racial immunity or lack of immunity to disease may be dietary rather than hereditary.

CONCLUSIONS

1. Excessive dental decay is an indicator of a gross dietary fault.

2. Odontoclasia (a type of decay of deciduous teeth) is associated with a high infant mortality and morbidity.

3. A diet in which the carbohydrates with an acid residue are replaced by alkaline starches and a small amount of vegetables is added results in a correction of the dental defect and apparently helps to lower the rate of infant mortality and morbidity.

EXTERNAL DIMENSIONS OF THE NEW-BORN

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There are relatively few recorded data on the external dimensions of new-born infants. A few dimensions were measured by Quetelet,[1] Daffner,[2] Weissenberg,[3] Friedenthal[4] and Schreiber.[5] The only extensive study reported in the literature is that of Kugler,[6] made in 1931.

Averages, standard deviations and coefficients of variation for thirty-three dimensions by sex and order of birth are shown in the table. The external dimensions are larger in males than in females and larger in later-born than in first-born infants. The proportion of the dimensions[7] to the total body length is identical in all the groups of new-born. There is no sex difference in the variability of the various dimensions.

SOCIAL STATUS

These measurements were made, for the most part, at Bellevue Hospital and the Fifth Avenue Hospital. Infants born at Bellevue Hospital come almost exclusively from poor homes, delivery and hospitalization being free, except in rare instances. Infants born at the Fifth Avenue Hospital, on the other hand, come from homes of moderate income, the parents being able to pay about $75 for the cost of delivery.

Infants born at Fifth Avenue Hospital are, on the average, larger in all the dimensions studied than those born at Bellevue Hospital. The

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From the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University and the Fifth Avenue Hospital.

1. Quetelet, L. A. J.: Anthropométrie ou mesure des différentes facultés de l'homme, Brussels, C. Muquardt, 1870, p. 342.

2. Daffner, F.: Das Wachstum des Menschen, ed. 2, Leipzig, Wilhelm Engelmann, 1902, p. 125.

3. Weissenberg, S.: Das Wachstum des Menschen nach Alter, Geschlecht und Rasse, Stuttgart, Strecker & Schröder, 1911.

4. Friedenthal, H.: Allgemeine und spezielle Physiologie des Menschenwachstums, Berlin, Julius Springer, 1914.

5. Schreiber, O. (Göttingen): Anthropologische Messungen an Neugeborenen, Ztschr. f. d. ges. Anat. **13**:675, 1928.

6. Kugler, E.: Körperproportionen und Kopfform bei Neugeborenen, Arch. d. Julius Klaus-Stiftg. f. Vererbgsforsch. **6**:429, 1931.

7. Calculations were made only for weight, bimalar diameter of face, biacromial and bi-iliac diameters and circumference of chest.

External Dimensions of the New-Born by Sex and Order of Birth

Dimension	First-Born Infants						Infants Born Later					
	Males (395 Cases)			Females (417 Cases)			Males (423 Cases)			Females (418 Cases)		
	Average, Mm.	Standard Deviation, Mm.	Coefficient of Variation, per Cent	Average, Mm.	Standard Deviation, Mm.	Coefficient of Variation, per Cent	Average, Mm.	Standard Deviation, Mm.	Coefficient of Variation, per Cent	Average, Mm.	Standard Deviation, Mm.	Coefficient of Variation, per Cent
Total body length	503.72	19.61	3.89	496.94	18.80	3.78	508.43	20.19	3.97	502.35	19.65	3.91
Body weight, Gm.	3,375.45	440.40	13.06	3,222.49	517.00	16.02	3,539.81	517.00	14.62	3,429.81	470.40	13.71
Sitting height	339.99	16.63	4.89	335.15	16.31	4.87	342.94	16.62	4.84	339.68	16.29	4.79
Circumference of head	344.90	12.14	3.52	338.52	13.39	3.96	347.61	13.55	3.90	340.68	11.69	3.43
Cephalic length	117.21	4.79	4.08	114.62	4.48	3.92	118.16	5.07	4.28	115.46	4.69	4.06
Cephalic breadth	92.78	4.09	4.41	91.87	4.06	4.42	93.71	4.30	4.59	92.46	4.22	4.57
Bimalar diameter of face	70.98	4.08	5.75	70.04	4.21	6.01	72.11	4.40	6.10	70.69	4.12	5.83
Bizygomatic diameter of face	73.10	4.10	5.60	71.96	3.76	5.22	72.86	5.53	7.58	72.93	4.07	5.58
Bigonial diameter of face	56.80	3.79	6.67	56.43	3.38	6.10	58.45	4.21	7.20	58.08	4.16	7.15
Height of upper part of face (nasion-prosthion)	31.87	1.92	6.02	31.15	1.95	6.26	32.21	2.23	6.94	31.38	2.09	6.63
Height of lower jow (infradentale mentor)	17.47	1.35	7.68	17.42	1.41	8.07	17.73	1.40	7.92	17.58	1.47	8.33
Height of nose	21.43	1.95	9.08	21.02	2.01	9.57	21.72	2.09	9.63	21.09	2.00	9.50
Breadth of nose	21.31	1.74	8.16	20.76	1.57	7.53	21.68	1.78	8.21	21.05	1.67	7.93
Inter-inner canthus	21.50	1.89	8.81	21.00	1.75	8.33	21.92	1.74	7.96	21.33	1.72	8.08
Length of ear	35.49	2.80	7.89	34.45	2.75	7.96	35.55	2.91	8.18	34.88	2.69	7.70
Breadth of ear	24.54	1.79	7.31	24.01	1.92	7.98	24.82	2.00	8.06	24.21	1.72	7.12
Biacromial diameter	112.48	7.82	6.95	111.30	7.10	6.37	114.93	7.45	6.51	113.81	7.36	6.47
Bi-iliac diameter	74.22	7.74	10.42	71.87	6.63	9.23	76.79	7.11	9.26	73.61	7.40	10.10
Circumference of thorax at the nipples	311.28	18.48	5.96	308.70	17.92	5.80	318.60	19.11	5.98	314.63	18.51	5.88
Length of hand	64.27	3.22	5.02	63.15	3.03	4.80	65.01	3.34	5.14	63.82	3.52	5.52
Length of palm	36.64	2.16	5.90	35.88	1.96	5.31	37.12	2.15	5.78	36.26	2.13	5.81
Breadth of palm	31.73	1.86	5.87	30.83	1.95	6.33	32.17	1.89	5.88	31.20	1.60	5.13
Length of middle finger	33.11	2.12	6.40	32.72	2.33	7.12	33.71	2.40	7.12	32.96	2.40	7.27
Length of lower extremity	218.47	10.15	4.63	216.71	10.46	4.81	220.12	10.46	4.75	218.39	10.72	4.91
	(71 Cases)			(79 Cases)			(62 Cases)			(49 Cases)		
Palpebral length	21.49	1.76	8.20	21.27	1.78	8.35	21.60	2.06	9.54	21.89	1.90	8.67
Length of humerus	86.23	4.67	5.42	84.46	4.46	5.29	86.69	6.48	7.47	85.09	6.39	7.50
Length of radius	71.68	3.48	4.86	70.37	3.57	5.08	73.19	4.57	6.25	73.01	4.03	5.52
Length of thigh	119.84	3.47	2.90	119.47	3.89	3.25	119.68	4.23	3.54	120.91	4.30	3.56
Length of tibia	86.85	5.07	5.83	85.34	4.89	5.75	87.94	6.19	7.05	87.50	6.30	7.20
Length of foot	78.90	3.76	4.77	77.80	3.25	4.17	80.07	4.18	5.22	79.93	3.88	4.86
Breadth of foot	30.44	1.62	5.32	29.45	1.85	6.27	31.11	2.19	7.04	30.26	2.21	7.30
Length from tibia to sole*	110.10	5.49	4.98	107.86	5.24	4.86	110.60	6.58	5.96	111.48	5.93	5.32
Length of span†	503.70	16.53	3.28	501.39	18.57	3.71	505.43	20.78	4.11	505.17	22.94	4.54

* The distance from the lower margin of the internal condyle of the femur to the sole, with the foot at right angles to the leg.
† The longest distance between the tips of the middle fingers, with the arms completely extended, the palms facing forward.

proportions of the dimensions to the total body length are identical in both groups. Williams [8] found that the average weight at birth of healthy full-term infants in his private practice was higher than that of white infants seen in hospital practice.

SEASONAL VARIATIONS

Calculations were made by season for twenty-four dimensions. The following dimensions showed seasonal changes, the dimensions being smaller during the spring and summer and larger during the autumn and winter: bimalar diameter of the face, height of the upper part of the face, height of the lower jaw, nasal height and breadth, biacromial diameter, bi-iliac diameter, circumference of the thorax and dimensions of the hand.

RACE OR NATIONALITY

Calculations were made for twenty-four dimensions by nationality of the parents (North European, Central European, Mediterranean and Jewish). No significant differences were found.

CORRELATION

Correlation coefficients were calculated separately by sex for twenty-four dimensions. The correlation between the total body length and the weight at birth is higher than in later life, as was shown by Pearson.[9]

The data on which the conclusions in this article are based will appear shortly in *Human Biology*.

Permission to make measurements on the new-born infants was given by Dr. Frederick Rice of Bellevue Hospital, Dr. Leon S. Loizeaux of the Fifth Avenue Hospital, Dr. Hervey C. Williamson of the New York Nursery and Child's Hospital and Dr. Caroline S. Finley of the New York Infirmary for Women and Children.

8. Williams, J. W.: Obstetrics, New York, D. Appleton & Company, 1921, p. 157.

9. Pearson, K.: Data for the Problem of Evolution in Man: III. On the Magnitude of Certain Coefficients of Correlation in Man, Proc. Roy. Soc., London **66**:23, 1900.

ANEMIA OF PREMATURITY

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The work reported in this paper is part of a study of the mechanism of anemia in infancy. The observations on the course of the changes in the hemoglobin and red cells in premature infants have been made with the purpose of studying the mechanism of the physiologic anemia of prematurity. All the babies comprising the study were in the wards of the Harriet Lane Home during the course of the determinations, and little attempt was made to follow them after they were discharged. Without a special mechanism in the clinic for insuring return visits, only those infants who are sick are returned for observation. For this reason many important practical questions will remain untouched in this work.

INVESTIGATIONS

Methods.—Hemoglobin was determined by the Newcomer method, and the hemoglobin values were reported in grams per hundred cubic centimeters. The color index is based on the percentage of hemoglobin and for this calculation 100 per cent of hemoglobin is equivalent to 14 Gm. per hundred cubic centimeters. For the determination of reticulocytes, slides were prepared with a film of cresyl blue considerably thicker than that used for the supravital staining of white cells, in order to obtain maximum reticulocyte counts. It was found that unless the nuclei of the white cells were well stained it was useless to expect good staining of reticulocytes. The counting of the reticulocytes was made in a wet preparation that had been allowed to stand for about twenty minutes. Several portions of the film were examined, but no portion was used in counting in which the film was thick enough to permit the formation of rouleaux. Any cell was considered a reticulocyte that had granules stained with cresyl blue even though a reticular structure might not be present.

I have gone into this question of the technic of reticulocyte counts in some detail because of the discrepancies between the counts reported in this paper and those in the literature. It is most probable that these discrepancies can be accounted for by differences in technic as well as by differences in the criteria for deciding what shall be considered a reticulocyte.

In presenting results, the patients have been divided into two groups, according to the weight at birth: Group 1 includes the infants weighing more than 1,700 Gm. at birth; group 2, those weighing 1,700 Gm. or less. Weight at birth was chosen as the criterion for the grouping rather than the degree of prematurity because of the difficulty of ascertaining the duration of gestation.

Explanation of Tables and Charts.—In order to simplify the presentation of the figures in the tables, it was found desirable to divide the total time of obser-

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From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics, Johns Hopkins University School of Medicine.

TABLE 1.—*Values for Hemoglobin and Reticulocyte Count for the Patients Whose Weight at Birth was Over 1,700 Gm.**

Patient	Weight at Birth		Ten Day Periods Beginning at Birth												
			1	2	3	4	5	6	7	8	9	10	11	12	13
1	1,800	Hgb*	19.0	14.7	....	....	....	....	....	....	....	....	....	....	....
		Ret	6.0	occasional											
2	2,300	Hgb	17.9	13.0	....	....	....	....	....	....	....	....	....	....	....
		Ret	....	occasional											
3	2,400	Hgb	17.4	13.4	....	....	....	....	....	....	....	....	....	....	....
		Ret	2.0	0.5											
4	1,750	Hgb	....	15.1	11.8	....	....	....	....	....	....	....	....	....	....
		Ret	....	occasional	occasional										
5	2,200	Hgb	13.7	9.9	9.0	11.0 Tr.	10.9	....	....	....	....	....	....	....	....
6	2,500	Hgb	15.1	17.1	....	11.5	....	....	....	....	....	....	....	....	....
7	2,300	Hgb	....	16.0	14.1	....	9.2	....	....	....	....	....	....	....	....
8	1,900	Hgb	....	13.9	11.2	7.7	7.8	9.8 L	....	....	....	....	....	....	....
		Ret	....	1.0	3.0	...	4.5								
9	2,000	Hgb	....	....	....	....	9.2	7.8	....	....	....	....	....	....	....
10	1,750	Hgb	....	....	....	9.4	9.0	7.0	....	Died of					
		Ret	....	....	....	occasional	occasional	infected		infection					
11	2,000	Hgb	....	18.5	....	11.2	10.9	9.5	8.7	....	....	....	....	....	....
		Ret	....	....	....	occasional	1.0		...						
12	1,800	Hgb	....	15.2	....	10.1	....	8.1	7.0	....	....	....	....	....	....
		Ret	....	....	....	1.5	....	7.0	...						
13	1,900	Hgb	....	15.7	....	11.5	....	9.1	8.7	9.4	....	....	....	....	....
		RBC§	....	4.80	....	3.65	....	3.20	3.25	3.15					
		Ret	....	0	....	2.5	....	5.0	4.0	3.0					
		CI§	....	1.16	....	1.13	....	1.03	0.96	1.06					
14	1,900	Hgb	....	....	....	....	9.8	9.5	9.2	9.2	....	....	....	....	....
		Ret	....	....	....	....	1.0	1.0	2.0	1.0					
15	1,800	Hgb	....	17.5	15.4	14.3	....	10.4	....	9.8	....	....	....	....	....
16	2,000	Hgb	....	....	....	14.6	....	12.6	....	....	11.0	....	....	....	....
17	2,200	Hgb	....	....	11.8	....	9.2	....	9.1	....	....	8.6	....	....	....
		Ret	....	....	....	....	....	....	5.0	....	....	1.0			
18	2,150	Hgb	....	....	14.0	12.4	10.2	....	....	....	8.5	8.0	7.9	7.5	9.8† C‡
		Ret	....	....	....	....	....	....	....	....	....	....	....	1.0	4.0 C

19	2,000	Hgb	....	....	....	**14.0**	11.2	11.2	....	8.1	7.0	 C	**9.8** C	....	....
		Ret	....	....	....	occasional	1.5	occasional	....	1.5	2.5	 C	**7.0**		
20	1,950	Hgb	....	....	....	....	....	9.0	....	7.7	**9.2**	**10.0**	....	....	....
		RBC	....	....	....	....	....	3.05	....	3.20	**3.70**	**3.90**			
		Ret	....	....	....	....	....	2.0	....	2.5	**5.0**	**3.0**			
		CI	....	....	....	....	....	1.05	....	....	**0.86**	**0.92**			
21	2,000	Hgb	....	....	....	....	....	....	....	7.7	**7.0**	**8.9**	....	....	....
		Ret	....	....	....	....	....	....	....	4.0	**1.5**	**2.5**			
22	1,750	Hgb	....	13.4	10.9 L‡	10.1 L	8.8 L	9.1 L	9.9 L	10.0 L	10.4 L	....	....	....	....
		Ret	....	occasional	occasional	0.5 L	0.5 L	3.5 L	....	....	....				
23	2,150	Hgb	....	13.0	**11.2**	9.8	**9.2**	**10.4**	....	....	....	....	....	....	....
		RBC	....	4.05	**3.75** L	3.25	**3.05** C	**3.95** C							
		Ret	....	0	**0.5**	1.0	**5.5**	**4.0**							
		CI	....	1.15	**1.07**	1.08	**1.08**	**0.94**							
24	1,750	Hgb	....	....	**11.9**	10.4	**8.1**	**9.8**	**9.7**	....	....	....	....	....	....
		RBC	....	....	**4.0**	3.45	**2.70**	**2.95**	**3.15**						
		Ret	....	....	**2.0**	3.0	**5.0**	**8.5**	**10.0**						
		CI	....	....	**1.06**	1.08	**1.07**	**1.18**	**1.10**						
25	1,800	Hgb	17.8	**17.6**	....	13.1	**10.0**	**10.1**	**11.3**	....	....	....	....	....	....
		RBC	5.20	**4.95**	....	4.30	**3.60** C	**3.85** C	**4.10** C						
		Ret	5.0	**1.0** L	....	1.5	**2.5**	**4.0**	**6.0**						
		CI	1.22	**1.27**	....	1.09	**0.99**	**0.94**	**0.99**						
26	1,800	Hgb	15.4	13.8	....	**10.4**	**9.4**	**10.5**	....	....	....	....	....	....	....
		Ret	3.0	occasional	....	**1.5**									
27	2,000	Hgb	....	....	16.0	**14.3**	**12.3**	**11.9**	**11.0**	**10.9**	....	....	....	....	....
		RBC	....	....	5.35	**4.20**	**3.80**	**3.75**	**3.70**	**3.70**					
		Ret	....	....	occasional	**1.0**	**1.5**	**2.0**	**2.0**	....					
		CI	....	....	1.07	**1.22**	**1.16**	**1.14**	**1.06**	**1.05**					
28	1,900	Hgb	17.7	16.2	13.6	**14.0**	**12.9**	**10.3**	**9.8**	....	....	....	....	....	....
		Ret	1.0	occasional	1.0	**1.5**	**1.5**	**2.5**	**2.5**						
29	1,800	Hgb	....	16.5	**14.8**	**13.6**	....	**9.8**	....	....	**8.9**	....	....	....	....
30	2,100	Hgb	14.0	**13.4**	**11.5**	**10.4**	....	**9.1**	....	....	....	....	....	....	....
31	2,200	Hgb	16.8	**15.2**	....	....	....	....	....	....	....	....	....	....	....
		Ret	3.0	**1.0**											
32	2,000	Hgb	15.5	**14.8**	....	**9.5**	....	....	....	....	....	....	....	....	....
		Ret	....	**1.0**	....	**2.5**									
33	1,750	Hgb	19.3	**19.6**	**16.5**	12.1	11.5	10.9	10.5	10.5	....	....	....	....	....
34	1,900	Hgb	19.6	15.4	13.4	10.6	....	....	....	....	....	....	....	....	....
		Ret	3.5	1.5	....	1.0									

* In this table and in table 2 the amount of hemoglobin (Hgb) is expressed in grams per hundred cubic centimeters, the reticulocytes (Ret) in per cent of the total red cell count.

† The figures in heavy type indicate the values for the periods succeeding the administration of iron.

‡ C indicates the beginning of the use of copper, and L, the use of liver.

§ RBC represents the number of red blood cells expressed in millions, and CI, the color index.

TABLE 2.—*Values for Hemoglobin and Reticulocytes for the Patients Composing Group 2, Whose Weight at Birth was 1,700 Gm. or Less*

Patient	Weight at Birth		Ten Day Periods Beginning at Birth																
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
35	1,600	Hgb	....	18.2	9.6	Died of infection														
		Ret	....	occasional	....															
36	1,600	Hgb	....	14.6	11.2	10.0	8.9	Died of infection												
		Ret	....	....	....	....	....													
37	1,650	Hgb	....	16.0	....	13.3	11.7	Died of infection												
		Ret	....	1.0	....	1.5	0.5													
38	1,500	Hgb	....	14.0	11.2	....	7.7	6.1	5.9	Died of infection										
		RBC	....	4.35	3.40	....	2.50	2.00	2.05											
		Ret	....	0.5	1.0	....	2.5	4.0	6.5											
		CI	....	1.15	1.03	....	1.10	1.09	1.02											
39	1,600	Hgb	....	....	....	15.1	12.6	9.5	8.5	....	....	....	....	....	....	....	....	....	....	....
		Ret	....	....	....	0.5	....	2.0	....											
40	1,400	Hgb	Trans-	19.8	18.2	....	10.6	8.1	7.0	6.3	....	Died of syphilis								
		Ret	fusion	0.5	....	....	3.0	3.0	5.5	3.5										
41	1,050	Hgb	Trans-	22.2	19.6	14.3	11.2	9.8	9.6	9.8	....	....	....	....	....	....	....	....	....	....
		Ret	fusion	0	....	3.0	....	2.5	....	6.0										
42	1,425	Hgb	....	12.5	10.9	....	8.8	8.1	....	8.4	....	....	....	....	....	....	....	....	....	....
		RBC	....	3.85	3.55	....	2.60	2.75	....	3.10										
		Ret	....	0.5	2.0	....	5.0	6.0	....	1.5										
		CI	....	1.14	1.08	....	1.12	1.05	....	0.97										
43	1,400	Hgb	21.2	....	....	....	9.6	....	8.4	....	8.7	....	....	....	....	....	....	....	....	....
		Ret	....	....	....	....	....	....	....	....	....									
44	1,400	Hgb	17.3	15.0	....	10.6	8.1	8.3	8.4	8.4	....	....	....	....	....	....	....	....	....	....
		RBC	5.1	4.35	....	2.95	2.65	2.85	3.10	3.15										
		Ret	10.0	1.0	....	3.0	3.5	5.5	7.0	5.0										
		CI	1.22	1.23																
45	1,500	Hgb	....	16.6	....	12.3	....	9.6	....	....	8.1	8.4	....	....	....	....	....	....	....	....
		Ret	....	....	....	....	....	0.5	....	....	3.0	1.5								
46	1,500	Hgb	....	....	14.0	....	8.8	....	8.1	....	....	7.3	7.7	....	....	....	....	....	....	....
		Ret	....	....	....	....	....	....	5.0	....	....	5.0	2.0							
47	1,700	Hgb	....	....	....	....	....	....	8.0	8.3	7.7	7.3	7.0	....	7.3	....	....	....	....	....
		RBC	....	....	....	....	....	....	2.60	2.75	2.65	2.75	2.85	....	3.05					
		Ret	....	....	....	....	....	....	3.5	2.0	4.0	5.0	....	....	2.5					
		CI	....	....	....	....	....	....	....	1.07	1.04	0.94	0.87	....	0.85					

48	1,350	Hgb	18.2	15.1	13.7	....	8.1	....	....	7.0	....	....	7.4	....	....	7.4	....	....	7.7	....
		Ret	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
49	900	Hgb	....	....	....	11.0	9.8	8.7	8.4	7.0	6.3	6.3	7.6	7.8	 C	7.8 C	8.7 L	8.2 L	8.7 L	10.1 L
		Ret	....	....	....	0	1.0	1.5	1.5	....	4.5	4.0	4.5	5.0	....	....	4.0	....	....	....
50	980	Hgb	....	....	....	....	....	....	6.7	6.7	8.7 L	8.4 L	9.8 L	10.1 L	10.1 L	 L	 L	10.6 L	....	....
		Ret	....	....	....	....	....	....	2.0	2.0	7.5	2.0	3.0	1.5	1.5	....	....	....		
51	1,350	Hgb	....	....	....	....	8.3	....	5.1	6.2	7.3	....	....	....	....	....	....	....	....	....
		RBC	....	....	....	....	2.75	....	1.95	2.45	2.80									
		Ret	....	....	....	....	2.5	....	4.0	9.0	4.0									
		CI	....	....	....	....	....	....	....											
52	1,690	Hgb	....	....	....	....	8.5	7.3	8.2	8.4	....	....	....	....	....	....	....	....	....	....
		RBC	....	....	....	....	3.40	2.65	2.80	3.05										
		Ret	....	....	....	....	3.5	3.0	7.0	3.5										
		CI	....	....	....	....	....	....	....											
53	1,500	Hgb	....	....	....	....	6.1	5.0	7.1		Died of syphilitic infection									
		Ret	....	....	....	....	4.0	6.0	5.5											
54	1,300	Hgb	....	....	....	9.8	7.6	6.2	5.9	6.4	6.7	7.0	....	8.9	8.9	....	....	....	....	....
		RBC	....	....	....	2.95	2.70	1.80	2.40	2.75	2.75	2.85	....	3.70	3.85					
		Ret	....	....	....	....	2.0	4.0	7.5	9.5	3.0	1.5	....	4.5	1.0					
		CI	....	....	....	1.18	1.00	1.22	0.88	0.84	0.87	0.88	....	0.86	0.82					
55	1,700	Hgb	22.4	17.4	....	12.4	9.8	9.0	8.7	10.0	10.9	....	....	....	....	....	....	....	....	....
		RBC	6.10	5.35	....	3.90	3.05	3.25	3.20 C	3.75 C	3.95 C									
		Ret	1.0	0	....	1.5	2.5	4.5	7.0	8.0	....									
		CI	1.31	1.15	....	1.04	1.14	0.99	0.97	0.95	0.99									
56	1,000	Hgb	....	18.4	15.9	12.2	10.1	9.1	9.0	9.1	9.9	9.5	9.3	....	12.1	....	....	....	....	....
		Ret	....	0	0	1.5	2.5	3.0	6.0	2.5	2.0	2.0	1.5	....	1.0					
57	1,500	Hgb	22.0	14.8	12.4	....	9.4	8.4	7.3	7.0	....	9.5	....	....	....	....	....	....	....	....
		Ret	3.0	....	0.5	....	1.5	1.5	2.0	5.0	....	6.0								
58	1,700	Hgb	....	14.0	11.5	10.0	9.2	7.8	8.7	9.8	10.4	....	....	....	....	....	....	....	....	....
		RBC	....	4.25	4.05	3.55	3.15	2.90 C	3.10 C	3.45 C	3.90 C									
		Ret	....	0.5	1.0	1.5	1.5	4.5	6.0	7.0	....									
		CI	....	1.18	1.01	1.01	1.05	0.98	1.01	1.02	0.95									
59	1,600	Hgb	....	....	15.2	13.7	9.6	9.2	8.7	9.2	9.6	10.0	....	....	....	....	....	....	....	....
		RBC	....	....	5.0	4.60	3.40	2.95	2.80	3.00	3.25	3.45								
		Ret	....	....	....	0.5	1.0	1.5	2.5	3.0	3.0	3.0								
		CI	....	....	1.09	1.06	1.01	1.11	1.11	1.10	1.05	1.03								
60	1,600	Hgb	....	....	13.4	8.7	9.7		Died of infection											
		RBC	....	....	4.30	3.25	3.50													
		Ret	....	....	1.0	2.0	5.0													
		CI	....	....	1.11	0.96	0.99													
61	1,500	Hgb	16.8	13.8	12.8	....	9.8	9.2	7.9	8.0	8.5	7.8	7.3	....	....	....	....	....	....	....
												Infection								
62	1,300	Hgb	20.0	15.4	12.2	11.8	10.6	8.7	8.5	7.8	....	....	....	....	....	....	....	....	....	....

vation, beginning at birth, into ten day periods, numbered 1, 2, 3 and so on in the tables. The figures for hemoglobin, the red cell count and the percentage of reticulocytes in each instance are those occurring at the midpoint of the ten day period. Naturally the figures were not always obtained on the fifth, fifteenth or twenty-fifth day of life, so that interpolation on a separate chart has been necessary, but no interpolated figure was used unless an actual figure had been obtained within the ten day period under consideration. When iron was given, the figures obtained in the succeeding periods are printed in heavy type. When the figures in heavier type begin with the fifth period, for example, it means that administra-

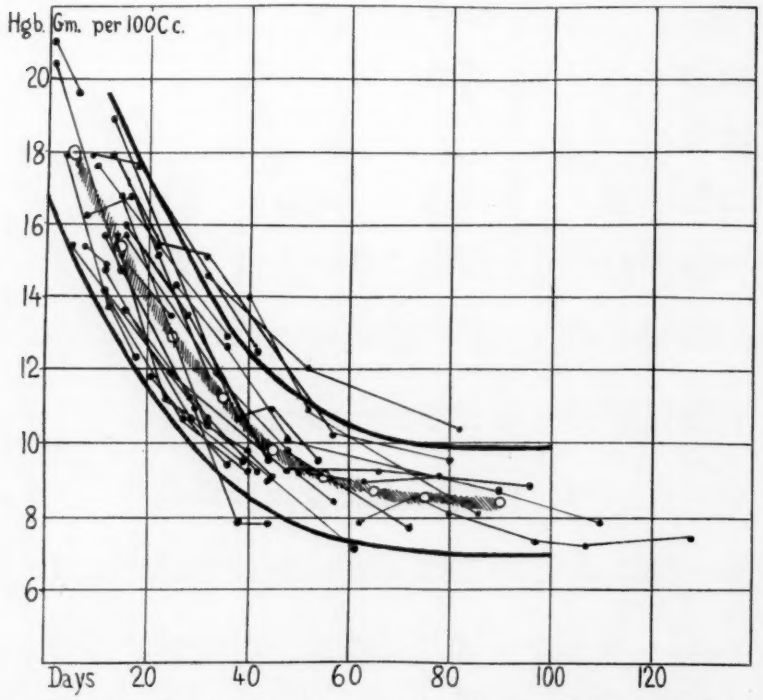

Chart 1.—Average hemoglobin curve and limits of variation for the untreated infants in group 1 weighing over 1,700 Gm. at birth. The chart includes curves for individual patients from which the average curve was constructed. In this chart and the following charts, the broad shaded line represents the curve for the average percentage of hemoglobin expressed in grams per hundred cubic centimeters; the continuous line with the solid dots represents the hemoglobin curves for the individual patients, and the medium heavy lines, the probable limits of the variation in the percentage of hemoglobin.

tion of iron was begun at some time between the thirtieth and the fortieth day of life. Similarly administration of liver is shown by the letter L placed in the period succeeding that in which the liver was first administered. This method of presentation has been used because of the presence of a latent period of from four to six days following the administration of liver or iron, so that the effect on the constituents of the blood is not to be expected immediately. Administration of

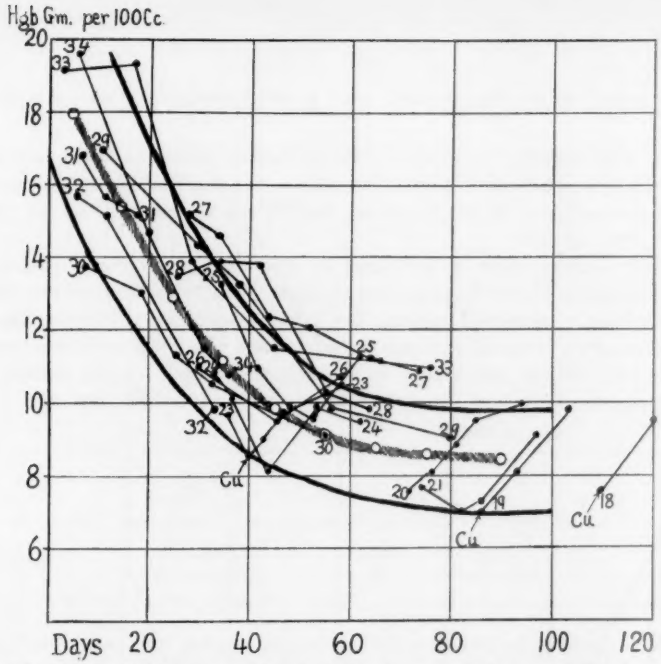

Chart 2.—Hemoglobin curves for individual patients in group 1 who received iron, plotted against the average hemoglobin curve and limits of variation for the untreated infants of the same group (chart 1). In this chart and in similar charts the curves for the individual patients start at the point at which iron was first administered. The numbers correspond to those of cases in the tables. *Cu* represents the point at which copper was given in cases 19 and 26.

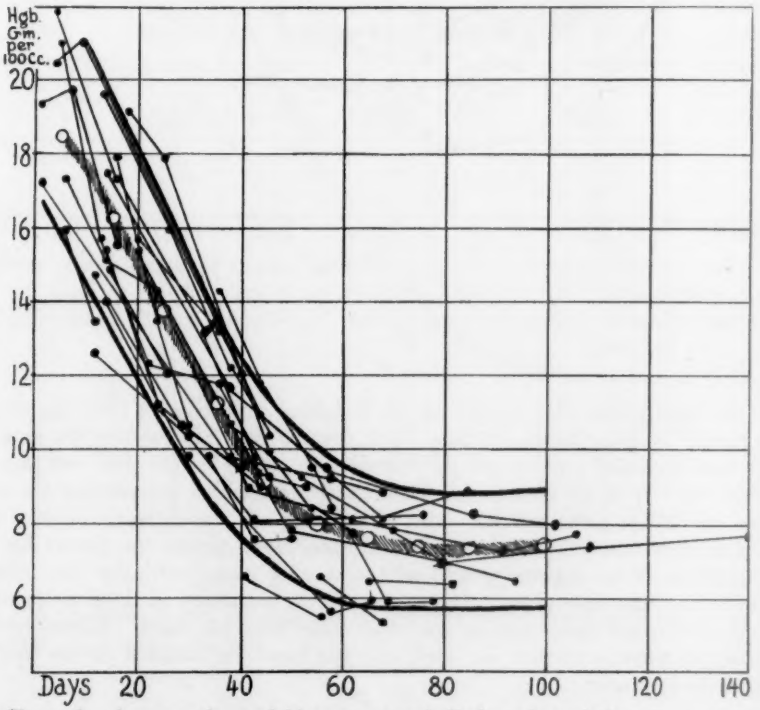

Chart 3.—Average hemoglobin curve and limits of variation for untreated infants of group 2 weighing less than 1,700 Gm. at birth. The chart includes the curves for individual patients from which the average curve was constructed.

copper is designated by the letter C. In the case of copper no latent period exists, so that the appearance of C means that copper was first administered at some time between the midpoint of the preceding period and the midpoint of the period in which C first appears.

For the demonstration of the effect of iron therapy on the hemoglobin, four charts were prepared, two for each group of cases. Charts 1 and 3 represent the curves for hemoglobin in untreated infants. The broad shaded line represents the average hemoglobin curve. In order to obtain the points from which this curve was constructed the actual figures for hemoglobin were averaged for each ten day period, and the average figures plotted on the fifth, fifteenth and twenty-fifth days and connected

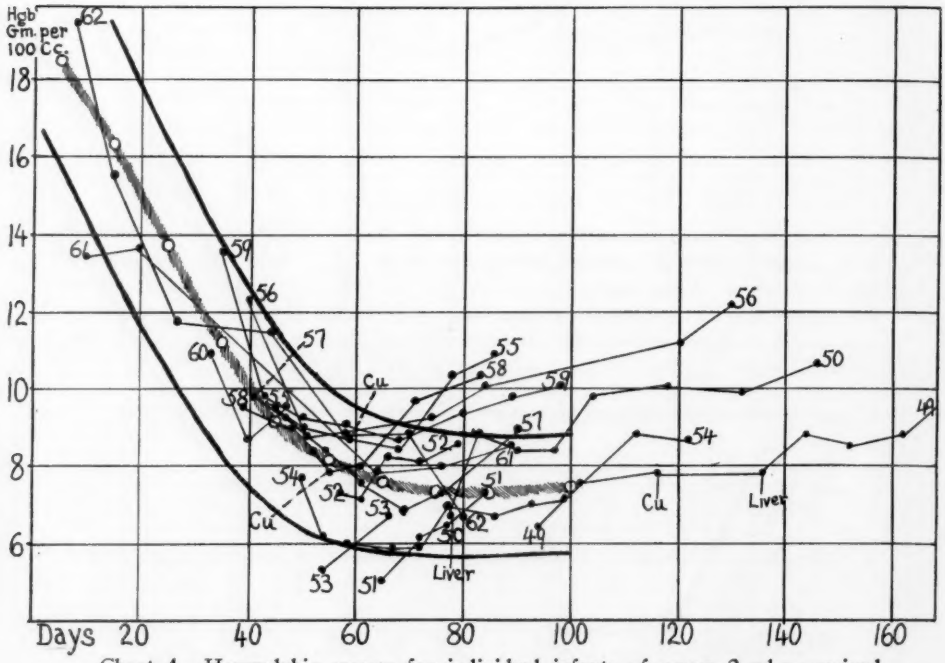

Chart 4.—Hemoglobin curves for individual infants of group 2 who received iron, plotted against the average hemoglobin curve and limits of variation for the untreated infants of the same group (chart 3). Copper and liver were used in the cases indicated.

by the shaded line. The figures for the individual patients were then charted and connected by thin, continuous lines. The medium lines representing the probable limits of variation were drawn by free hand to include within their compass the great majority of the points. In charts 2 and 4 the curves representing the average hemoglobin value and the limits of variation for the untreated infants were copied from charts 1 and 3, and against these were plotted the figures for the hemoglobin in the patients treated with iron, each curve starting at the point at which iron was first given. These curves were numbered in order to facilitate reference to the tables and to the other more detailed charts. When liver or copper in addition to iron was used, this fact has been indicated on the chart in an obvious manner.

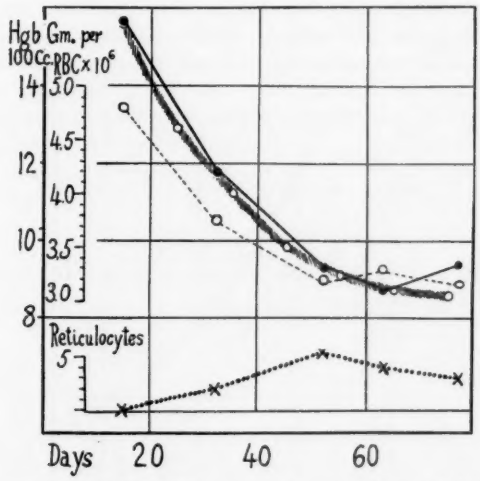

Chart 5.—Curves for patient 13, group 1, an untreated infant. The curve for the number of red blood cells is indicated by hollow circles with a broken line; that for the reticulocytes, by a heavy dotted line with crosses.

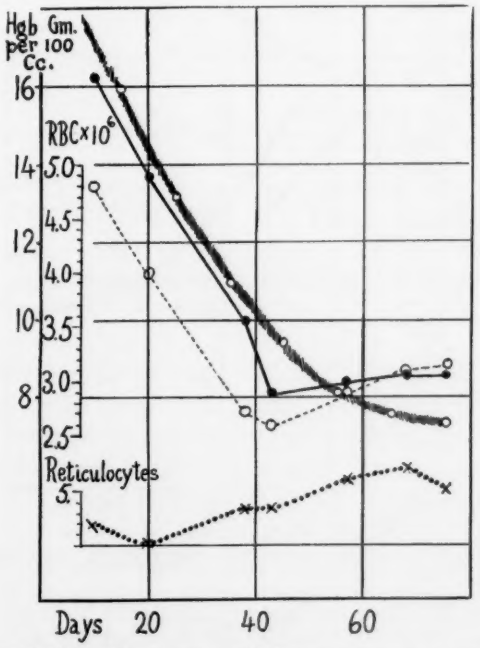

Chart 6.—Hemoglobin, red cell and reticulocyte curves for patient 44, group 2, who was not treated with iron.

To emphasize certain points, individual charts have been prepared. In these the hemoglobin in grams per hundred cubic centimeters is designated by solid circles connected by a continuous line, the red cells by hollow circles connected

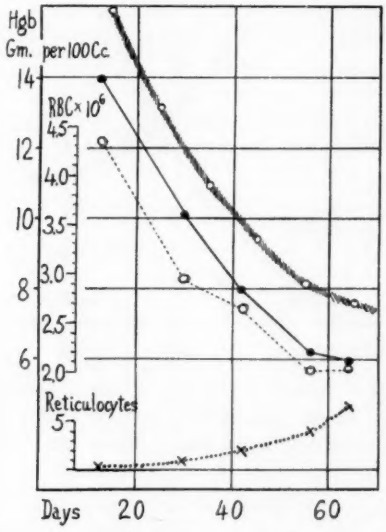

Chart 7.—Curves for patient 38, group 2, an untreated infant.

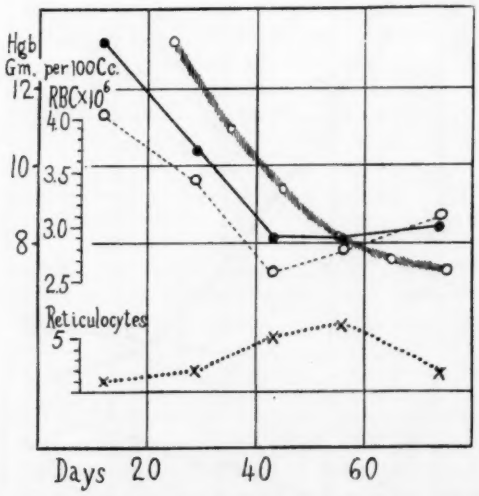

Chart 8.—Curves for patient 42, group 2, an untreated infant.

by a broken line and the percentage of reticulocytes by crosses connected by a heavy dotted line. The broad shaded line represents the curve for the average percentage of hemoglobin in the untreated infants taken from charts 1 and 3. The chart is so constructed that when the color index is 1 the values for the red cells and hemoglobin coincide.

Dosages.—Iron was given as ferric ammonium citrate in a 10 per cent solution, 2 cc. daily per kilogram of body weight. Copper was given as a 0.5 per cent solution of crystallized copper sulphate, 1 cc. daily per kilogram of body weight, in divided doses in the milk. Liver was given in the form of a raw or slightly cooked emulsion of scraped liver, 5 cc. daily per kilogram of body weight. All the babies received some form of milk diet and in addition either viosterol or cod liver oil and after four or five weeks orange juice.

RESULTS OF THERAPY

Effects of Iron.—From a consideration of charts 1, 2, 3 and 4, one may conclude that iron with or without a supplement of liver or copper

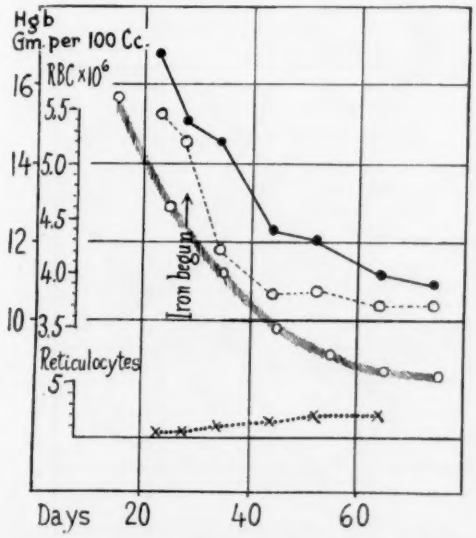

Chart 9.—Curves for patient 27, group 1, to whom iron was given early, before the thirtieth day. Note the hemoglobin curve lying well above the average and the failure of the response of the reticulocytes.

is capable of raising the hemoglobin. There are, however, other observations to be made from these charts. It is evident that the hemoglobin curves for the untreated patients of group 2 (chart 3) tend to reach definitely lower values than those for group 1 (chart 1). Neither group of patients showed a demonstrable tendency for the average hemoglobin to rise during the period for which sufficient figures are available, although in a few individual cases a slight tendency to rise may be seen. From charts 2 and 4 it may be seen that for a certain length of time, iron has no demonstrable effect on the hemoglobin curve; then at about the fortieth day for group 1 and somewhat later for group 2, there occurs a general sweeping upward of the curves. The curves for the patients to whom iron was given early tend to lie above the average for untreated

infants, without any sudden change in direction, while in those for babies treated later, in whom the hemoglobin had reached lower values, the rise is sharp. In general, the lower the hemoglobin when iron takes effect, the sharper the rise.

Red Cells and Color Index.—The color index tends to be high in the first few weeks of life and then gradually falls until at about the third month of life it varies around 1. In this study there are no figures for the color index beyond the third month of life. Figures in the literature point to a rise in the number of red cells without an accompanying rise in the amount of hemoglobin, so that the color index

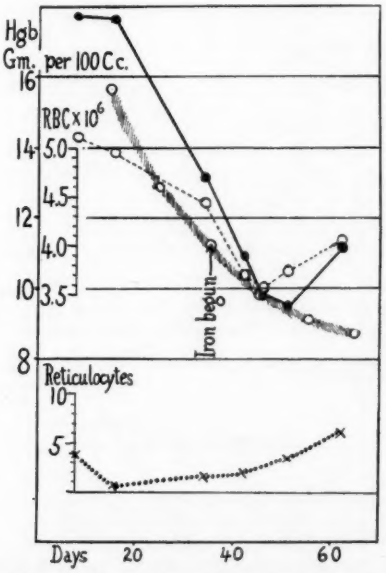

Chart 10.—Hemoglobin, red cell and reticulocyte curves for patient 25, group 1. The administration of iron was begun later than in the case of patient 27 (chart 9), between the thirtieth and fortieth day. Note the delayed response both of the red cells and hemoglobin and of the reticulocytes.

undergoes a further reduction. That this fall in the color index after the third month of life must take place is evident from the fact that the severe anemia seen later in premature babies is always of the hypochromic type, with a very low color index. The normal occurrence of a high color index in the first three or four months must be remembered before too much importance is attached to the occurrence of a high color index in anemia at this age.

Reticulocytes.—It has been amply demonstrated that the reticulocyte counts are relatively high at birth (from 8 to 10 per cent) and fall rapidly during the first week or ten days of life. The data in this paper

include only a few counts made in the first few days of life, but they show well the virtual disappearance of reticulocytes after the tenth day. Reticulocytes reappear after a few weeks and gradually increase in number as the hemoglobin falls, reaching their highest values as the hemoglobin curve flattens (charts 5, 6, 7 and 8). When the data for the infants treated with iron are considered, the relation of the effect of iron, the rise in red cells and hemoglobin and the rise in reticulocytes is well demonstrated. Charts for individual patients have been used for the purpose of showing this rise (charts 9, 10, 11, 12, 13, 14, 15 and 16). To certain of these patients copper was given in addition to iron. Copper, however, had no effect that could be demonstrated, so for the pur-

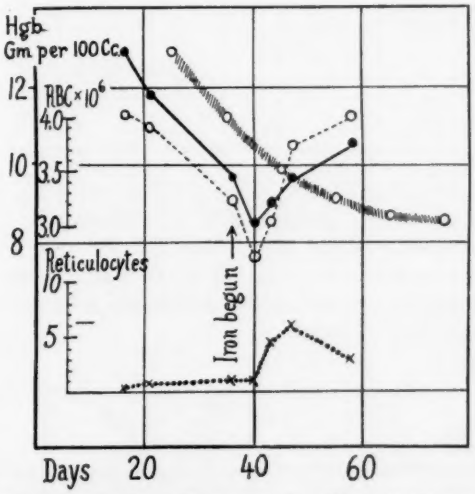

Chart 11.—Curves for patient 23, group 1. The administration of iron was begun close to the fortieth day. Note the almost immediate response of the red cells, hemoglobin and reticulocytes.

poses of this study its use has no significance. It is, of course, necessary in interpreting the charts to consider group 1 and group 2 separately.

From these charts it may be seen that iron given early to the infants in the first group (chart 9) and to those of the second group (chart 12) was without influence on the rise of reticulocytes, while the number of red cells and the percentage of hemoglobin tended eventually to remain higher than in the untreated infants. When the administration of iron was begun somewhat later (chart 10 for group 1 and charts 13 and 14 for group 2), there occurred a gradual rise in reticulocytes with a maximum count several weeks after the iron was started. When the administration of iron was further delayed, the response of the reticulocytes tended to become more prompt (chart 11 for group 1 and chart 15 for group 2), until finally the response was immediate, as in chart 16.

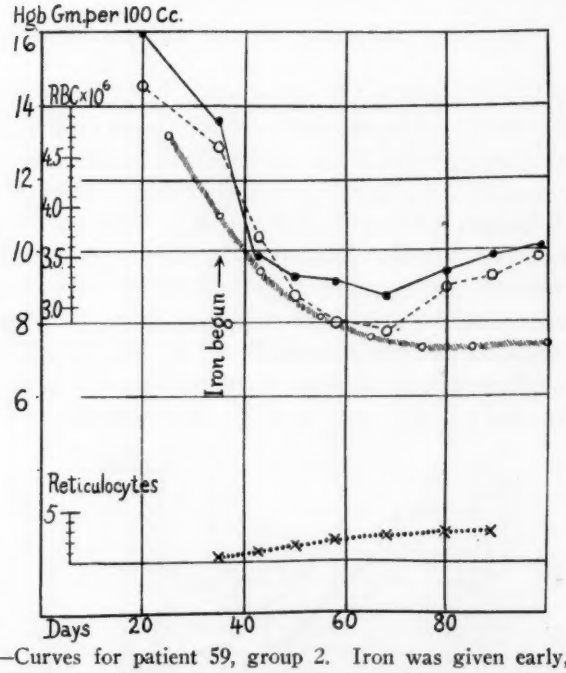

Chart 12.—Curves for patient 59, group 2. Iron was given early, before the fortieth day. Note the failure of response of the reticulocytes, with a slight and delayed rise in the number of red cells. Note also that iron given at about the fortieth day was followed by little response in this case, whereas in the cases of the patients in group 1 iron given at this period was followed by an immediate or an only slightly delayed response.

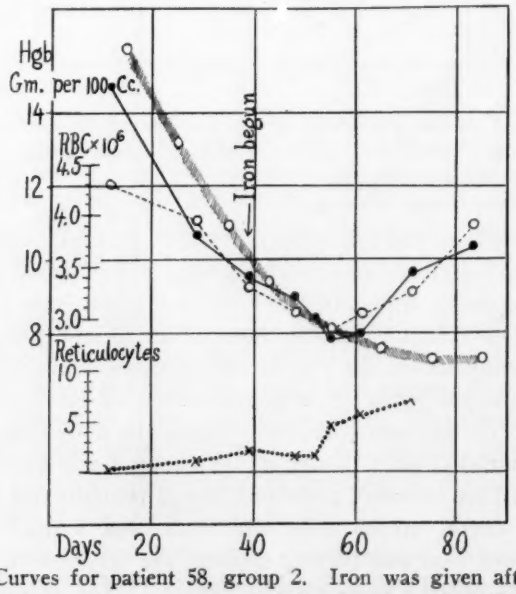

Chart 13.—Curves for patient 58, group 2. Iron was given after the fortieth day. Note that the response was more definite than in patient 59 (chart 12) but was much more delayed than in the patients of group 1 to whom iron was given at about the fortieth day.

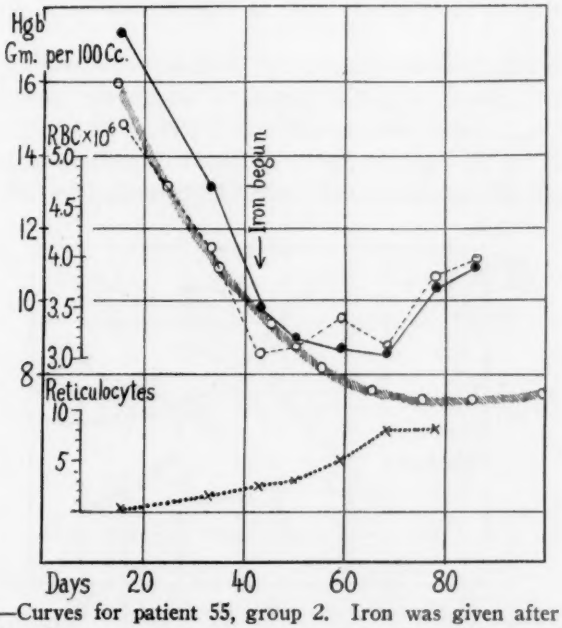

Chart 14.—Curves for patient 55, group 2. Iron was given after the fortieth day. Note that the response of reticulocytes, red cells and hemoglobin was still considerably delayed.

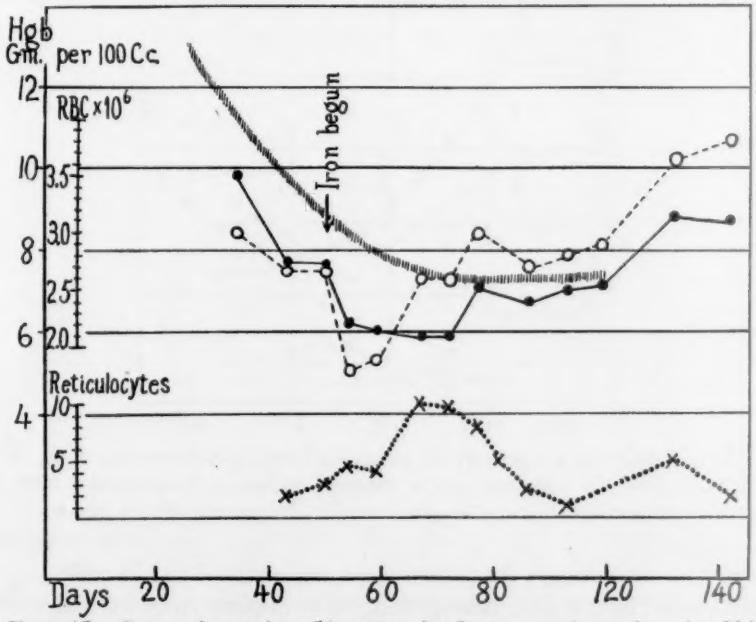

Chart 15.—Curves for patient 54, group 2. Iron was given after the fiftieth day. Note that the response of the reticulocytes and red cells was only slightly delayed. The response in this patient corresponds to that in the patients of group 1 to whom iron was administered from about the fortieth day.

There are two factors to be considered in these cases: the time at which iron was first given, and the degree to which the hemoglobin was reduced. Occasionally, the second may be the factor that determines the course of the hemoglobin curve. Thus in case 60, in which iron was given the infant fairly early and in which the hemoglobin was low com-

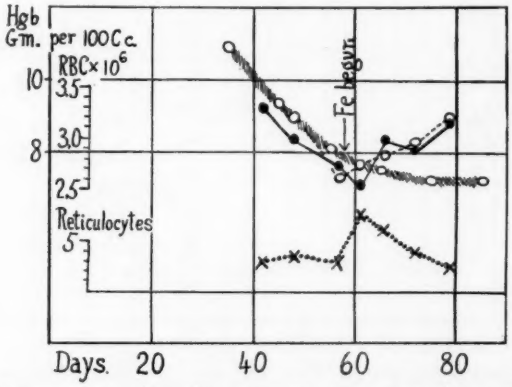

Chart 16.—Curves for patient 52, group 2. Iron was given after the sixtieth day. Note the immediate response of the reticulocytes, red cells and hemoglobin.

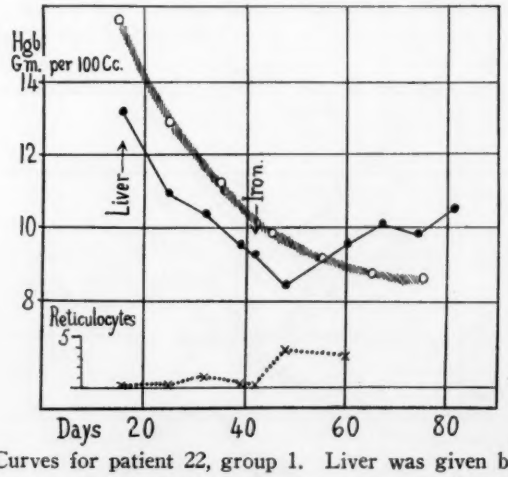

Chart 17.—Curves for patient 22, group 1. Liver was given before the twentieth day. Note the complete lack of response to liver. The response after the later administration of iron is the usual one for the patients of this group.

pared with the average, there occurred a well marked rise in reticulocytes accompanied by a rise in hemoglobin. It is evident from the charts that there is a close relation between the response of the reticulocytes and the rise in red cells and hemoglobin, though a close quantitative relation between the degree of the response of the reticulocytes and the rapidity of the rise in red cells and hemoglobin cannot always be demonstrated.

As a result of these observations, two periods in the development of the physiologic anemia of prematurity may be considered; an early period, characterized by a rapidly falling hemoglobin content and red cell count and a failure of response to iron, and a later period, in which the hemoglobin content and the red cell count of untreated babies remain

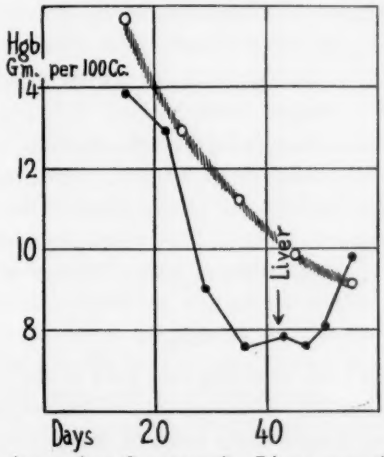

Chart 18.—Curves for patient 8, group 1. Liver was given after the fortieth day. Note that the response to liver given alone is no different from that to iron.

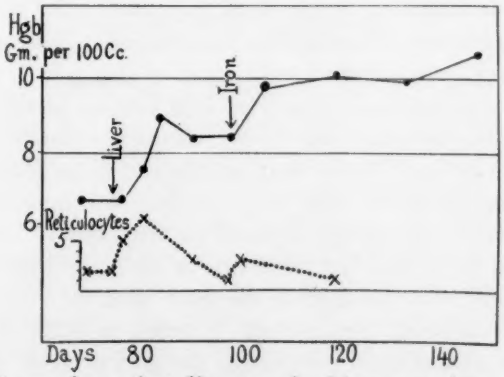

Chart 19.—Curves for patient 50, group 2. Liver was given after the seventieth day. Note that as in patient 8 (chart 18) the response to liver given alone was the same as that to iron. In this patient iron was followed by a slight additional response.

at a low figure or rise slightly but respond well to iron therapy. Between these two periods is one of transition, during which there is a delayed response to iron. The less the infant weighs at birth and therefore, presumably, the greater the prematurity, the later the period of transition tends to occur.

Effect of Liver and Copper.—Liver, either as an emulsion or as an extract, had no effect when given in the early period alone or as a supplement to iron (patients 22, 23, 25; chart 17). In two infants to whom it was given later alone it had an immediate effect similar to that of iron. In the case of one infant (patient 49) to whom after a long period of iron therapy it was given as a supplement to iron it apparently initiated a rise that might not otherwise have occurred, but in two other cases there was no demonstrable effect. The observations are, of course, too few to allow any conclusions to be drawn regarding the value of liver as a supplement to iron.

There is no evidence that addition of copper is of any value. Nor should one expect any result from copper. Previous work [1] indicated that copper increases the rate of formation of hemoglobin but has no other effect on hemopoietic activity. In these cases the high color index suggests that there is no disturbance in the formation of hemoglobin.

COMMENT

It is clear that lack of iron plays no part in the development of the anemia up to the beginning of the period of transition. In considering the effect of iron given later there must be taken into account two more or less separate functions of iron: (1) as a building material for hemoglobin and (2) as a stimulator of hemopoietic activity. Since the fall in hemoglobin at first is more rapid than the rise in weight, it is evident that the total hemoglobin of the body is considerably reduced by the time the concentration of hemoglobin has reached its lowest value. Iron is, therefore, set free. Undoubtedly some of this iron is excreted, but judging from the results of a study of iron balance in full term babies, which is yet to be published, and from Lichtenstein's study on premature babies,[2] the major part of this iron is retained to be used later in the formation of hemoglobin. How long this iron will be available for the formation of new hemoglobin depends on the rapidity of growth and the presence of infections, but there can be no doubt that at the end of the early period (from the sixth to the tenth week of life) iron is available for the formation of hemoglobin. It seems probable, therefore, that the chief value of medicinal iron during the period under discussion lies in its stimulating effect. The fact that liver was able to produce a similar stimulation accompanied by a rise in hemoglobin is confirmatory of this point of view.

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1. Josephs, H. W.: Mechanism of Anemia in Infancy, Bull. Johns Hopkins Hosp. **51**:185, 1932.

2. Lichtenstein, A.: Der Eisenumsatz bei Frühgeborenen, Acta pædiat. **1**: 194, 1921.

Lichtenstein [3] points out two periods in the anemia of prematurity: a period lasting about three months during which the anemia is hypoplastic, followed by a period in which the anemia is chlorotic owing to the failure of iron depots. The present paper deals only with Lichtenstein's early period of three or four months before the chlorotic type of anemia begins to develop, but from the data presented one may conclude that the hypoplastic stage does not last for more than two months and is followed by a period in which recovery takes place when the hemopoietic tissue is stimulated.

"Hypoplasia" is a term that requires definition, for it is evident that it is not used in a strict anatomic sense. The rise in reticulocytes in untreated infants, reaching its maximum at about the period of transition, indicates a reactive hemopoietic tissue but one in which the reaction is inadequate to the needs of blood formation. The principal characteristic of the early period is not the absence of reticulocytes, as in an aplastic anemia, but the failure of a response of the reticulocytes to iron. It is the appearance of such a response of the reticulocytes that characterizes the transition from the early to the later period. What causes the inadequacy in the early period is not known. Studies are being carried out on the rate of blood destruction in premature babies which promise to throw light on this question. That this inadequacy of the hemopoietic tissue is ordinarily not a serious matter is shown by the relative infrequency of nucleated red cells, such as occur in some cases of syphilis or in cases of severe hemolytic anemia, in which the inadequacy of the hemopoietic tissue is much greater.

EFFECT OF INFECTIONS AND SYPHILIS

Some attempt has been made to exclude from the series from whose hemoglobin values averages were computed patients in whom an infection was present. This objective has been attained probably only when the infection was obvious, for the dividing line between a slight and no infection is not sharp. One must accept the cases as they come, and if mild infection is so common as to be inseparable from the picture of prematurity it would be creating an artificial standard to exclude such cases. In comparing the results obtained in this study with those of other investigators, this must be taken into account, and it is possible that better mechanisms for avoiding infections, such as incubators or a special air-conditioned room, might easily account for the higher hemoglobin values reported from other clinics. Likewise patients with obvious syphilis were excluded. Those for whom the figures have been

3. Lichtenstein, A.: Hämatologiska studier å för tidigt födda barn, Stockholm, 1917.

used had no symptom other than a slight coryza in addition to the positive reaction to the Wassermann test on which the diagnosis was based.

As may be seen from the tables, the majority of the babies that eventually died of an infection had low hemoglobin values before the fatal infection developed. This might mean that they had mild, subclinical infections for a considerable time, but in the absence of fever or evidence of infection such a conclusion is scarcely justifiable. It is much more likely that these babies were what might be termed "poor risks" from the beginning and that their low hemoglobin content was a reflection of a condition that also rendered them liable to infection. Of course, it is possible that a low hemoglobin content in itself might have rendered the infant more open to infection, but in two cases a rise in hemoglobin that followed administration of iron had not the least influence on the fatal course. Two cases are of course not sufficient to furnish conclusive evidence that a low hemoglobin content is not an important contributory factor in the development of an infection, but, on the other hand, there is no clear evidence that it is a factor. Transfusion was more successful in the treatment of infection, and it was felt that this measure averted a fatal outcome even in severe cases, so that transfusion should remain the method of choice in treating infants in whom the hemoglobin content is markedly below the average.

The mild type of syphilis present in the patients included in this series behaved as a nonsyphilitic infection, and in the absence of any infection other than syphilis the prognosis was no worse than that of the average case. This suggests that mild syphilis has little direct influence on the blood, but acts indirectly by rendering the infant more susceptible to infections of the upper respiratory tract.

SUMMARY

A group of premature babies has been studied during the first three or four months of life, for the purpose of determining, if possible, the mechanism of the physiologic anemia of prematurity. Importance has been attached to the response of the reticulocytes and especially its relation to the administration of iron. From the study of the reticulocytes it was concluded that there is no basis for the idea that the fall in red cells and hemoglobin was dependent on hypoplasia in any strict anatomic sense. There was a period of failure to react to the administration of iron that lasted for from six to ten weeks after birth, the duration of the period depending largely on the degree of prematurity. After this early period of nonreactivity there followed a short transition period with delayed response, after which administration of iron was followed by a prompt response of the reticulocytes and a rise in red cells and hemoglobin. There is no reason to believe that lack of stores

of iron plays any part in the development or persistence of the anemia before the end of the third month. Thereafter, the rise in red cells without a corresponding rise in hemoglobin in untreated infants indicates the possibility that lack of stores of iron has become an important factor. From the results reported here one cannot conclude that a low percentage of hemoglobin is in itself harmful, although it probably is indicative of a condition that renders the infant more likely to succumb to infection. In such cases, although iron may raise the hemoglobin content, transfusion must still remain the method of choice in treating the condition as a whole. The evidence from this study does not permit the conclusion that liver is necessary as an adjunct to iron, though in individual cases it may prove of benefit. As in the case of iron, liver given alone in the early period was ineffective, but given later was followed by a response which differed in no way from that following the administration of iron. Copper had no demonstrable effect.

RICKETS

CONTROL WITH FIFTY UNITS (STEENBOCK) OF COD LIVER OIL VITAMIN D CONCENTRATE IN MILK

DONALD J. BARNES, M.D.
DETROIT

Standardization of potency of antirachitic substances by rat assay has, with the introduction of antirachitic agents other than cod liver oil or its concentrates, lost much of its value through the discovery that the relative prophylactic amounts of these different substances for rats, chickens and infants are not comparable unit for unit. No such dissimilarity was suspected during the time that irradiated products were first being developed until it was found that viosterol, when used for rats, chickens and infants, fell entirely out of line with what was known concerning the preventive dose of cod liver oil for the three species [1] named. Irradiated milk now seems to be demanding a still further revision of ideas concerning vitamin D effectiveness [2] as measured in rat units. While viosterol measured in rat units when compared to cod liver oil seems relatively impotent,[3] for infants irradiated milk seems to be just the reverse, its relative effectiveness being claimed to be higher, according to rat assay of potency,[2] than that of cod liver oil.

The amount of viosterol, expressed in rat units, required by the infant has during the past few years received considerable attention, while few studies in which present assay methods are used have been made of the minimum requirements of cod liver oil. An investigation reported in 1929,[3a] in which 3 teaspoonfuls of cod liver oil were used for prophylaxis, included rat assays of the oil, but the dosage was based on the observations of Eliot,[4] who found by trial

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One Steenbock unit is equal to approximately 2.7 U. S. P. X (1934) revised) units of vitamin D.

1. Steenbock, H.; Kletzien, S. W. F., and Halpin, J. G.: The Reaction of Chickens to Irradiated Ergosterol and Irradiated Yeast as Contrasted with the Natural Vitamin D of Fish Liver Oils, J. Biol. Chem. **97**:249 (July) 1932.

2. Hess, A. F., and Lewis, J. M.: An Appraisal of Antirachitics in Terms of Rat and Clinical Units, J. A. M. A. **101**:181 (July 15) 1933.

3. (*a*) Barnes, D. J.; Brady, M. J., and James, E. M.: The Comparative Value of Irradiated Ergosterol and Cod Liver Oil as a Prophylactic Antirachitic Agent when Given in Equivalent Dosage According to Rat Units of Vitamin D, Am. J. Dis. Child. **39**:45 (Jan.) 1930. (*b*) DeSanctis, A. G., and Craig, J. D.: Comparative Value of Viosterol and Cod Liver Oil as Prophylactic Antirachitic Agents, J. A. M. A. **94**:1285 (April 26) 1930.

4. Eliot, M. M.: The Control of Rickets, J. A. M. A. **85**:653 (Aug. 29) 1925.

and observation that this dose was most satisfactory, no rat assay being made on the cod liver oil that she used. Accepted standards for cod liver oil are still based on clinical opinion [5] rather than on controlled observational material. Until more definite clinical standards are available for cod liver oil, the relative values of cod liver oil, viosterol and irradiated milk cannot be adequately expressed. The most recent statement [2] gives the following as equivalent dosage:

	Units
Irradiated milk	40
Viosterol	600
Cod liver oil	240

Such a comparison, expressed in rat units, seems premised on the old standard of 3 teaspoonfuls of cod liver oil a day as a proper prophylactic dose for a baby—an amount determined empirically at a time when that amount of cod liver oil contained about 150 rat units of vitamin D, instead of 240 units, as do the good oils of today.

The following report contains data bearing on the aforementioned question, obtained with vitamin D milk made by incorporating a vitamin D concentrate of cod liver oil in milk and indicates that such conclusions are based on a fallacy. The study was begun before the introduction of irradiated milk in purchasable form and the publication of recent data on it, and consequently my observations were made only on the cod liver oil concentrate in milk. It would be highly desirable to have a comparison of results when different types of vitamin D milk are used by infants under the same conditions and at the same time.

Eliot and others have indicated the great need of a reasonably priced antirachitic agent easily available to all classes of population. She showed that salmon oil,[6] although at present not commercially available in sufficient quantities, has a high antirachitic potency, and that it might, with some revision of industrial practice, be made available at a low cost. From the point of view of public health, this entire line of thought is of the utmost importance. With the possibility of a low price and certain advantages in distribution, it was felt that a vitamin D milk, with the added advantage of its palatability and nearly automatic administration for infants, was well worth investigating.

During the winter of 1932 and 1933 further observations were made on the amount of vitamin D necessary for prophylaxis of rickets. My

5. Council on Pharmacy and Chemistry of the American Medical Association: Average Optimal Dosage of Cod Liver Oil, J. A. M. A. **98**:316 (Jan. 23) 1932.

6. Eliot, M. M.; Nelson, E. M.; Souther, S. P., and Cary, M. K.: Value of Salmon Oil in Treatment of Infantile Rickets, J. A. M. A. **99**:1075 (Sept. 24) 1932.

preliminary studies [7] with a commercial cod liver oil concentrate [8] homogenized in milk indicated that 150 units, or even 110, was more than necessary for prophylaxis in the average infant. In the study described here, I therefore aimed to approach the minium prophylactic dose of cod liver oil vitamin by ascertaining the effect of 50 units of the concentrate when given in the medium of milk.

The group consisted of thirty-eight infants from the Child Welfare Clinics of the Detroit Health Department who were observed through the winter. A daily dose of 50 units of vitamin D was given each baby, and this was maintained in spite of individual variations in the amount of milk used in formula feeding by the addition of the proper amount of cod liver oil concentrate to 1 pint (473 cc.) of milk. Each infant received a pint of the special milk every day and, if more milk was needed, plain pasteurized milk was added in sufficient quantity to make the formula. Therefore, irrespective of the total quantity of milk in the day's feeding, the amount of concentrate remained the same. The special milk was prepared under careful supervision [9] by the addition of a specified number of rat units of vitamin D concentrate to a small amount of milk by means of a small homogenizing apparatus, which thoroughly incorporated the vitamin D materials in the milk.[10] This special mixture was then mixed completely with the remainder of the milk in such quantity that each pint contained the requisite amount, namely, 50 Steenbock units of vitamin D.[11] The intake of milk and the methods of making the formulas were carefully checked in the field several times during each two week period between clinic visits by a nurse who devoted her full time to the study and who consequently was able to evaluate the degree of cooperation obtained through her intimate home association. Only cooperating families were included, the rest being dropped from the experiment.

In the group studied, nineteen infants were under 6 months of age, eleven under 4 months and the remaining nineteen between 6 and 12

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7. Barnes, D. J.: Antirachitic Concentrates, J. Michigan M. Soc. **32**:242 (April) 1933.

8. Zucker, T. F.: Further Observations on the Chemistry of Cod Liver Oil, Proc. Soc. Exper. Biol. & Med. **20**:136, 1922-1923. Addition of Vitamin D Concentrate to Milk, Am. J. Pub. Health **23**:10 (Jan.) 1933.

9. The patents for the cod liver oil concentrate are under the control of Columbia University.

10. Committee on Food of the American Medical Association: Vitamin D Fortified Pasteurized Milk (150 Vitamin D Units per Quart) Advertising of W. J. Kennedy Dairy Company, J. A. M. A. **101**:34 (July 1) 1933.

11. The potency of the concentrate received an additional check through biologic assays conducted on market samples of vitamin D milk. The concentrate used in my special milk was the same as that used in the commercial product. The biologic assays were conducted by C. A. Hoppert, Ph.D., of the department of physiological chemistry at Michigan State College.

months. The average age at the start of the observation was 3.64 months, eight of the infants entering the study in November and thirty in December. None had had antirachitic therapy before the special milk containing cod liver oil vitamin D concentrate was given other than some casual exposure to sunlight during the summer. Twenty-five of the babies were white, and thirteen were colored. Roentgen examination [12] of the long bones (wrist and knee) was made approximately every two weeks to determine any rachitic state, present or developing. At the start, since work commenced late in the fall, six babies showed slight rickets. This disappeared, as roentgen examination revealed, during the next few weeks, and no new cases developed during the study.

TABLE 1.—*Summary*

Number of infants in experimental group		38
Race: White		25
Colored		13
Average age: At beginning of study	3.64 months	
At end of study	10.65 months	
Roentgenographic findings: Normal throughout		32
Rachitic on first examination		0
Healed at end of study		6
Number of infants in control group		25
Race: White		13
Colored		12
Average age; (at end of study, i. e., at time of roentgen examination)	6.2 months	
Roentgenographic findings; Rachitic	14 (56%)	
Nonrachitic	11 (44%)	

The gains in weight were in general satisfactory, the gain averaging approximately 1 pound (0.5 Kg.) a month. Detailed data are given in the tables. Intercurrent infections occurred among the group, as would be expected, but no unusual problems in nutrition developed, though the infants were from poverty-stricken homes.

In April the collection of a group of control cases was started. A total of twenty-five babies, taken without selection as they appeared at the clinic, were examined by roentgen rays. They had had no antirachitic treatment during the winter, as they had not come under clinical supervision, and therefore afforded a suitable standard for comparison with the study group. Thirteen were white, and twelve were colored. Their average age was 6.23 months; they did not differ in age materially from the experimental group at the end of the period of study. Of the controls, fourteen (56 per cent) were rachitic, and eleven

12. The roentgenograms were made at the Children's Hospital of Michigan and interpreted by Dr. E. R. Witwer.

TABLE 2.—*Prevention (Normal Infants Receiving 50 Units [Steenbock] of Vitamin D per Day in the Form of Vitamin D Milk)*

Name, Race, Date of Birth	Date of Examination	Weight Lbs.	Weight Oz.	Roentgen Findings
L. J.	11/28/32	12		Negative
White	12/12/32	12	6	Negative
9/23/32	12/29/32	12	15	Negative
	1/12/33	13	6	Negative
	1/26/33	14	3	Negative
	2/16/33	14	14	Negative
	3/ 7/33	15	7	Negative
	3/23/33	15	14	Negative
	4/ 3/33	16	10	Negative
	4/24/33	16		Negative
D. L.	1/ 7/33	14	5	Negative
White	1/21/33	15	9	Negative
6/21/32	2/ 4/33	16		Negative
	2/18/33	16	8	Negative
	3/ 4/33	16	15	Negative
	3/30/33	17	5	Negative
	4/13/33	18	2	Negative
	4/27/33	18	4	Negative
E. D. M.	1/ 5/33	9	9	Negative
White	1/19/33	10	9	Negative
11/19/32	2/ 2/33	11	1	Negative
	2/16/33	12	2	Negative
	3/ 2/33	13		Negative
	3/16/33	13	12	Negative
	4/ 6/33	15	5	Negative
	4/20/33	15	12	Negative
D. M.	1/ 5/33	14	10	Negative
Colored	1/21/33	14	7	Negative
7/19/32	2/ 2/33	15	1	Negative
	2/14/33	15	2	Negative
	2/21/33	16		Negative
	2/28/33	16	5	Negative
	3/12/33	17	11	Negative
	3/28/33	18	1	Negative
	4/ 8/33	17	12	Negative
	4/22/33	17	15	Negative
D. M.	1/ 5/33	21	13	Negative
White	1/19/33	22	6	Negative
3/10/32	2/ 2/33	22	15	Negative
	2/16/33	23	2	Negative
	3/ 2/33	23	10	Negative
	3/16/33	24	2	Negative
	3/30/33	24	2	Negative
	4/13/33	24	5	Negative
	4/27/33	25		Negative
L. S.	1/ 3/33	23	7	Negative
Colored	1/14/33	23	8	Negative
1/3/32	1/28/33	23	13	Negative
	2/11/33	23	11	Negative
	2/25/33	24	5	Negative
	3/11/33	25		Negative
	3/30/33	25		Negative
	4/18/33	25	12	Negative
J. W.	12/30/32	15	11	Negative
White	1/21/33	16	12	Negative
8/16/32	2/18/33	17	12	Negative
	3/18/33	19	2	Negative
	4/22/33	20	3	Negative
S. S.	12/29/32	18	11	Negative
White	1/12/33	18	7	Negative
3/1/32	2/ 4/33	20	5	Negative
	2/18/33	20	11	Negative
	3/ 4/33	21	14	Negative
	3/23/33	22	1	Negative
	4/10/33	22	5	Negative
	4/27/33	22	10	Negative
A. C.	12/29/32	11	2	Negative
White	1/16/33	11	7	Negative
8/1/32	2/ 2/33	11	13	Negative
	2/28/33	12		Negative
	3/28/33	13		Negative
	4/ 8/33	13	3	Negative
	4/29/33	*		Negative
M. R.	12/29/32	17	15	Negative
White	1/12/33	18	5	Negative
3/17/32	1/26/33	19	9	Negative
	2/16/33	20	4	Negative
	3/ 6/33	20	5	Negative
	3/25/33	20	9	Negative
	4/ 8/33	20	14	Negative
	4/20/33	21	14	Negative
F. M.	12/28/32	18	4	Negative
White	1/11/33	18	3	Negative
3/7/32	2/18/33	19	9	Negative
	3/ 4/33	19	12	Negative
	3/18/33	19	14	Negative
	4/ 7/33	22		Negative
	4/22/33	21		Negative
F. C.	11/28/32	17	12	Negative
White	12/12/32	18	8	Negative
3/13/32	12/27/32	18	14	Negative
	1/10/33	19	1	Negative
	1/24/33	19	1	Negative
	2/ 7/33	19	6	Negative
	2/21/33	19	7	Negative
	3/ 7/33	20	3	Negative
	3/28/33	20	1	Negative
	4/11/33	20	12	Negative
	4/25/33	21	3	Negative
F. E. W.	11/29/32	19		Negative
White	12/12/32	20	6	Negative
2/16/32	12/27/32	21		Negative
	1/16/33	21	10	Negative
	1/30/33	21	14	Negative
	2/ 4/33	21	15	Negative
	2/14/33	22	1	Negative
	3/ 4/33	22	8	Negative
	3/23/33	23		Negative
	4/ 4/33	23	5	Negative
	4/18/33	22	14	Negative
E. M. W.	11/29/32	16	4	Negative
White	12/21/32	17	3	Negative
5/26/32	1/ 4/33	17	3	Negative
	1/21/33	17	7	Negative
	2/22/33	18	11	Negative
	3/ 9/33	19	10	Negative
	3/30/33	20		Negative
	4/13/33	20	9	Negative
	4/28/33	21		Negative
J. Z.	11/30/32	9	7	Negative
White	12/17/32	10	5	Negative
10/13/32	1/ 3/33	10	9	Negative
	1/17/33	10	7	Negative
	1/31/33	11	2	Negative
	2/14/33	12	4	Negative
	3/ 9/33	13	5	Negative
	3/23/33	13	9	Negative
	4/ 6/33	13	15	Negative
	4/20/33	14	7	Negative
D. P.	12/ 1/32	15	15	Negative
Colored	12/17/32	16	2	Negative
6/2/32	12/31/32	16	4	Negative
	1/14/33	17		Negative
	1/28/33	17	13	Negative
	2/11/33	18	8	Negative
	2/25/33	18	14	Negative
	3/11/33	20		Negative
	3/25/33	20	1	Negative
	4/ 8/33	20	3	Negative
	4/20/33	20	4	Negative
P. C.	12/ 1/32	16	7	Negative
White	12/30/32	16	15	Negative
5/5/32	1/14/33	17	4	Negative
	1/28/33	17	3	Negative
	2/11/33	17	9	Negative
	2/25/33	17	9	Negative
	3/11/33	17	13	Negative
	3/18/33	18	2	Negative
	4/ 1/33	18	14	Negative
	4/22/33	19		Negative

* Not taken.

TABLE 2.—*Prevention (Normal Infants Receiving 50 Units [Steenbock] of Vitamin D per Day in the Form of Vitamin D Milk)—Continued*

Name, Race, Date of Birth	Date of Examination	Weight Lbs.	Weight Oz.	Roentgen Findings
J. M. C.	12/ 1/32	19	2	Negative
Colored	12/17/32	19	13	Negative
4/1/32	1/ 5/33	20	6	Negative
	1/21/33	21	1	Negative
	2/ 7/33	21	8	Negative
	2/23/33	21	15	Negative
	3/ 9/33	22	6	Negative
	3/18/33	22	8	Negative
	4/ 8/33	22	12	Negative
	4/22/33	22	8	Negative
C. L.	12/ 2/32	9	12	Negative
Colored	12/17/32	10	6	Negative
9/1/32	1/ 9/33	11	4	Negative
	1/24/33	11	14	Negative
	2/14/33	12	5	Negative
	2/28/33	13		Negative
	3/23/33	14	11	Negative
	4/ 7/33	15	8	Negative
	4/22/33	16	1	Negative
A. L.	12/ 2/32	13	8	Negative
Colored	12/16/32	14	15	Negative
8/2/32	1/ 7/33	16	4	Negative
	1/21/33	17	6	Negative
	2/ 4/33	17	5	Negative
	2/14/33	17	6	Negative
	2/28/33	17	3	Negative
	3/12/33	18	14	Negative
	3/29/33	20	4	Negative
	4/11/33	20	1	Negative
	4/25/33	20	4	Negative
R. R.	12/ 3/32	8	14	Negative
White	12/31/32	9	8	Negative
9/8/32	1/14/33	10	14	Negative
	2/ 2/33	11	9	Negative
	2/22/33	12	6	Negative
	3/13/33	14		Negative
	3/25/33	14	13	Negative
	4/18/33	15	8	Negative
	4/22/33	16	12	Negative
M. Z.	12/21/32	19		Negative
White	1/14/33	20	5	Negative
(Twin)	1/28/33	21	3	Negative
2/23/32	2/11/33	21	7	Negative
	2/25/33	21	8	Negative
	3/11/33	21	14	Negative
	4/ 1/33	23	2	Negative
	4/22/33	22	15	Negative
J. Z.	12/21/32	23		Negative
White	1/ 3/33	23	1	Negative
(Twin)	1/14/33	24		Negative
2/23/32	1/28/33	24	7	Negative
	2/11/33	24	5	Negative
	2/25/33	24	7	Negative
	3/11/33	24	14	Negative
	4/ 1/33	25		Negative
	4/22/33	25	8	Negative
D. D.	12/17/32	10	8	Negative
White	12/31/32	11	6	Negative
9/20/32	1/17/33	12	7	Negative
	1/31/33	13	3	Negative
	2/14/33	13	2	Negative
	3/ 7/33	14		Negative
	3/28/33	14	12	Negative
	4/11/33	15	6	Negative
	4/25/33	16	1	Negative
R. S.	12/17/32	18	8	Negative
Colored	1/ 6/33	19	12	Negative
3/26/32	1/21/33	20		Negative
	2/18/33	21		Negative
	3/ 4/33	21	2	Negative
	3/16/33	21	9	Negative
	3/28/33	22	3	Negative
	4/ 8/33	22	7	Negative
	4/22/33	22	11	Negative
L. S.	12/13/32	15		Negative
White	12/27/32	15	8	Negative
8/3/32	1/12/33	16	2	Negative
	2/21/33	18	7	Negative
	3/ 7/33	18	10	Negative
	3/28/33	19	7	Negative
	4/13/33	19	1	Negative
	4/29/33	19	8	Negative
J. T.	12/12/32	16	3	Negative
White	1/17/33	17	2	Negative
8/25/32	2/ 2/33	17	9	Negative
	2/21/33	18	1	Negative
	3/27/33	19		Negative
	4/27/33	20	3	Negative
E. W.	12/ 8/32	22	12	Negative
Colored	12/22/32	23	4	Negative
2/20/32	1/ 5/33	23	15	Negative
	1/19/33	24	1	Negative
	2/ 2/33	24	6	Negative
	2/23/33	25		Negative
	3/ 9/33	25	8	Negative
	3/23/33	25	4	Negative
	4/18/33	26	4	Negative
D. T.	12/ 8/32	12	1	Negative
Colored	12/22/32	12	5	Negative
8/30/32	1/ 9/33	12	11	Negative
	1/24/33	13	3	Negative
	2/ 9/33	14	4	Negative
	2/23/33	14	8	Negative
	3/ 9/33	15	3	Negative
	3/18/33	15	7	Negative
	4/ 1/33	16	5	Negative
	4/15/33	16	15	Negative
	4/30/33	17	14	Negative
C. C.	12/ 6/32	14		Negative
White	12/20/32	13	14	Negative
8/28/32	1/ 3/33	14	6	Negative
	1/17/33	15	3	Negative
	1/31/33	16		Negative
	2/14/33	16	3	Negative
	2/28/33	16	8	Negative
	3/12/33	17		Negative
	3/28/33	17	4	Negative
	4/18/33	17	4	Negative
	4/25/33	17	3	Negative
J. W.	12/ 5/32	12	6	Negative
Colored	12/20/32	12	7	Negative
7/7/32	1/ 9/33	11	9	Negative
	1/28/33	12	10	Negative
	2/16/33	13	1	Negative
	3/ 2/33	12	15	Negative
	3/16/33	11	12	Negative
	3/28/33	12	6	Negative
	4/11/33	12	14	Negative
	4/25/33	13	8	Negative
D. H.	12/10/32	19	8	Negative
Colored	12/24/32	19	13	Negative
12/21/31	1/ 7/33	19	9	Negative
	1/21/33	20	4	Negative
	2/ 4/33	20	6	Negative
	2/18/33	20	13	Negative
	3/ 4/33	20	7	Negative
	3/18/33	20	13	Negative
	3/30/33	20	12	Negative
	4/13/33	21	11	Negative
	4/27/33	22	3	Negative

TABLE 3.—*Healing (Rachitic Infants Receiving 50 Units [Steenbock] of Vitamin D per Day in the Form of Vitamin D Milk)*

Name, Race, Date of Birth	Date of Examination	Weight Lbs.	Weight Oz.	Roentgen Findings
B. C.	11/28/32	14	1	Mild rickets
Colored	12/12/32	14	5	Mild rickets
7/12/32	12/27/32	14	15	Mild rickets
	1/10/33	15	11	Healing
	1/24/33	15	14	Healing
	2/ 7/33	16	6	Healed
	2/21/33	16	14	Negative
	3/ 7/33	17	6	Negative
	3/21/33	18	4	Negative
	4/ 4/33	18		Negative
	4/18/33	18	7	Negative
D. R.	11/29/32	17	8	Mild rickets
Colored	12/29/32	17	5	Healing
4/9/32	1/19/33	17	7	Healing
	2/ 2/33	18	1	Negative
	2/21/33	17	12	Negative
	3/ 7/33	19	2	Negative
	3/21/33	19	12	Negative
	4/ 4/33	20	2	Negative
	4/25/33	20	14	Negative
J. F.	11/30/32	13	6	Mild rickets
White	12/16/32	14	3	Mild rickets
8/1/32	1/ 5/33	15		Mild rickets
	1/26/33	15	14	Healing
	2/21/33	16	10	Healing
	3/ 8/33	17		Healed
	3/23/33	17	5	Negative
	4/12/33	17	14	Negative
	4/30/33	18	4	Negative
G. M.	12/ 3/32	18	11	Mild rickets
White	12/29/32	19	8	Mild rickets
4/25/32	1/21/33	20	7	Healing
	2/18/33	21	7	Healing
	4/22/33	23	2	Healed
G. W.	12/12/32	15	10	Mild rickets
White	12/27/32	16	4	Mild rickets
7/4/32	1/10/33	16	11	Mild rickets
	1/24/33	16		Healing
	2/14/33	16	12	Healing
	3/ 4/33	17	10	Healed
	3/18/33	18	5	Negative
	4/ 8/33	19	3	Negative
	4/22/33	19	7	Negative
D. C.	12/31/32	17	2	Mild rickets
White	1/17/33	18	1	Mild rickets
6/20/32	2/18/33	19		Healing
	3/ 9/33	19	14	Healing
	3/18/33	20		Healed
	4/ 4/33	20	3	Negative
	4/15/33	20	9	Negative
	4/24/33	20	13	Negative

TABLE 4.—*Controls*

Name	Date of Birth	Weight Lbs.	Weight Oz.	Race	Date of Roentgen Examination	Results Positive	Results Negative
W. Z.	4/13/32	21	2	White	3/15		—
Cl. R.	8/29/32	26	8	Colored	3/28	+	
J. G.	12/27/32	11	12	Colored	3/ 4	++++	
D. T.	11/ 7/32	17	1	White	3/ 4	+	
A. R.	9/ 3/32	18		White	3/ 9		—
E. S.	1/11/32	20	10	Colored	3/ 7		—
A. C.	9/18/32	17	14¾	White	3/ 7	+	
A. McK.	12/22/32	8	8	Colored	3/11	+++	
B. McR.	9/11/32	18	6¼	Colored	3/16	+	
W. McG.	10/29/32	..		White	3/22		—
T. M.	11/12/32	13	4	White	3/25		—
E. W.	12/ 5/32	12	10½	Colored	3/28	+	
J. S.	7/—/32	15	11¼	White	3/28	+	
C. T.	8/21/32	14	6½	White	3/30	+++	
J. B.	9/15/32	18	8	Colored	3/30	+	
J. C.	12/30/32	..		Colored	4/ 3		—
Ev. B.	8/ 8/32	17	3	White	4/ 4	+	
Q. N.	3/17/32	10	8	White	4/ 5		—
A. A.	8/16/32	15		White	4/ 5		—
D. W.	12/18/32	13		White	4/ 7		—
G. G.	1/ 1/33	12	2	White	4/14	+	
R. M.	1/ 4/33	6	10	Colored	4/17		—
A. H.	3/13/32	..		Colored	4/19		—
C. R.	11/27/33	14	15¾	Colored	4/19	++	
E. B.	9/12/32	18	6½	Colored	4/29	+++	
						14 Pos.	11 Neg.

(44 per cent) nonrachitic, as determined by roentgen examination. These percentages agree well with the control group I observed in 1929,[3a] 51 per cent of whom were found to be rachitic after going through the winter without antirachitic treatment.

COMMENT

As has been mentioned, the relative requirement of vitamin D for the infant has been expressed as 40 rat units for irradiated milk and 240 rat units for cod liver oil.

As previously emphasized, any estimate of the requirements of vitamin D for infants at present rests on comparatively few data. It is obviously not an easy task to collect these in sufficient numbers to allow even reasonable statistical treatment, and in recent studies in which comparisons of various antirachitic agents were made, this is particularly evident. There has also been a strong tendency to neglect the actual ascertainment of the minimum dose. Furthermore, an element of doubt has been introduced into studies of vitamin D as a whole by findings which showed that viosterol did not by any means have the expected effect in infants. Considerable time passed before it was realized that in viosterol one is probably dealing with a substance that is not at all the same as the factor originally designated by McCollum as vitamin D. In a survey of the field, a recent report by Christensen,[13] director of the Agricultural Experiment Station, University of Wisconsin, discussed natural and artificial forms of vitamin D, stating that: "These differences . . . are not due to the presence of other constituents in cod liver oil but are caused by a difference in vitamins." The opinion was also expressed: "that the differences between the natural and artificial vitamin D have to do with quantity rather than quality."

It is therefore a matter of great interest that irradiated milk and "yeast milk," [2] both of which involve artificial irradiation and therefore do not come under the Wisconsin classification of "natural vitamin D," are claimed to be as active as, or even more active than, the "natural vitamin D" of cod liver oil. This might be interpreted as indicating that besides the "natural" cod liver oil, vitamin D and viosterol, there are also other active artificial antirachitic substances.

From a chemical point of view it seems premature even to discuss identity or nonidentity of vitamin D produced by various means, since

13. Christensen, C. L.: Forty-Ninth Ann. Rep. Agric. Exper. Stat., University of Wisconsin, 1932, p. 2, line 14; p. 3, line 4.

apparently the structure of not one of them has been worked out.[14] To judge by physiologic action, however, it is perfectly definite that one form of artificial vitamin D, namely, "viosterol," has properties quite different from the factor originally designated as vitamin D. The properties of the antirachitic factor of irradiated milk, on the other hand, seem to resemble those of natural vitamin D more closely.

In clarifying the situation one must not only give more attention to the determination of the minimum dose but also consider the form in which vitamin D is given. Its degree of dispersion and its physical environment may play a large rôle. Janes and others [15] have indicated that the degree of dispersion of fat-soluble physiologically active substances is of importance, and Hess also alluded to this in discussing the action of vitamin D in irradiated milk. Further, a standardized clinical technic for gathering data is as essential as a proper laboratory procedure if satisfactory comparisons are to be made.

CONCLUSIONS

1. Thirty-two normal infants were completely protected against rickets from November or December to April on 50 units of vitamin D given as a concentrate in milk.

2. Six infants entering the study with slight roentgenographic signs of rickets showed progressive improvement on 50 units of vitamin D in milk a day. Since the rachitic lesions were slight, the healing processes were not striking, but they were nevertheless definite when traced throughout the series of roentgenograms. In no case did the patient grow worse during the study.

3. A control group of twenty-five infants without antirachitic treatment during the winter were examined by roentgen rays in April. Fourteen, or 56 per cent of these, showed active rickets, the remainder being normal.

4. It is shown that for comparison of the various forms of vitamin D the ratio 40 : 240 for the vitamin D or irradiated milk and the vitamin D of cod liver oil does not hold. When both are given in milk the required units are approximately equal. Considering the relatively small

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14. (*a*) Askew, F. A.; Bruce, H. M.; Callow, R. K.; Philpot, J. St. L., and Webster, T. A.: Nature **128**:758, 1931. (*b*) Windaus, A. H., and Leittringhaus, A.: Ueber das bestrahlte Ergosterin, Deutsche med. Wchnschr. **58**:1669 (Oct. 21) 1931. (*c*) Bills, C. E., and McDonald, F. G.: Crystalline Vitamin D, J. Biol. Chem. **96**:189 (April) 1932.

15. Janes, E. R.; Grover, H. F., and Quinn, E. J.: Method of Enhancing the Vitamin A Value of Cod Liver Oil, Proc. Soc. Exper. Biol. & Med. **30**:516 (Jan.) 1934. Bills and McDonald.[14c]

number of infants, the error of biologic assay [16] and the difficulty of quantitative clinical evaluation, it is not safe to say that one differs from the other.

5. A standardized clinical procedure is necessary in order to make satisfactory quantitative comparisons of various antirachitic substances.

The Child Welfare Division of the Detroit Health Department, the Detroit Department of Public Welfare and the Staff of the Children's Hospital of Michigan cooperated and assisted with this study.

16. Although rat assays present their difficulties, the large numbers done in various laboratories during the last few years have led to a sufficient knowledge so that when a large enough number of animals is used an acceptable accuracy can be attained. The usual commercial standardization is ±15 per cent; while the use of many more animals would give better results, such practice is infrequent.

PHOSPHATASE STUDIES

V. SERUM PHOSPHATASE AS A CRITERION OF THE SEVERITY AND RATE OF HEALING OF RICKETS

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Kay [1] demonstrated that plasma phosphatase was relatively high in rickets. The maximum value which he found in this condition was about seven times his average for normal children of the same age, and about eleven times his average for the normal adult.

Using our procedure for the determination of serum phosphatase,[2] in which certain errors in Kay's method have been avoided, we found that serum phosphatase in rickets reached about twenty times the average for normal children and about sixty times the average for normal adults.[3] We discussed some typical results, including effects of

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From the Laboratory Division, Hospital for Joint Diseases.

1. Kay, H. D.: Plasma Phosphatase: II. The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. **89**:249 (Nov.) 1930.

2. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase. Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93 (June) 1933.

3. For reasons explained elsewhere [10] our respective phosphatase figures in adults should be used, whenever possible, as a basis of comparison of clinical data obtained by Kay's method and ours. The following brief consideration of the methods used may explain, in part, the differences between Kay's results and ours: As is well known, the hydrolysis of a substrate is increasingly retarded by the products of hydrolysis. Kay's (J. Biol. Chem. **89**:235 [Nov.] 1930) method for the determination of plasma phosphatase generally involved the use, in each test, of 15 mg. of sodium beta-glycerophosphate, equivalent to about 1.5 mg. of inorganic phosphorus. In other cases Kay apparently used the equivalent of 2.5 mg. and in still others about 3.2 mg. of phosphorus. The incubation period was forty-eight hours. It is evident from Kay's figures that when the plasma phosphatase activity was high large proportions of the substrate were hydrolyzed during the long period of incubation. Consequently, the rate of hydrolysis was increasingly retarded by the products of hydrolysis and very considerable minus errors were caused. Kay used oxalated plasma. We have found that the phosphatase activity of oxalated plasma is about nine tenths of the serum phosphatase activity when about 2 mg. of potassium oxalate is used with 1 cc. of blood. We use serum for phosphatase determinations, incubating 1 cc. at 37 C. with 10 cc. of a substrate containing

(Footnote continued on next page)

treatment with cod liver oil and viosterol, at the twenty-sixth annual meeting of the American Society of Biological Chemists in 1932,[4] at the December 1933 session of the Section of Pediatrics of the New York Academy of Medicine, and in a symposium on enzymes at the Cleveland meeting of the American Chemical Society, September 1934. After we had completed most of our work, Smith and Maizels [5] and Smith [6] reported their plasma phosphatase figures in rickets. They used a modification of Kay's method for determination of phosphatase, and their ratios of phosphatase figures in rickets to those found in normal children were similar to his.[7]

We ascribe our higher ratios partly to the avoidance of certain analytic errors. It is probable, however, that they are due in some measure to differences in clinical material. With few exceptions, our patients with marked rickets were Negro children. In these patients ordinary exposure (of face and extremities) to sunlight had mitigated the effect of the dietary deficiency even less than in white children, and a relatively higher incidence of rickets was thus favored. It may be relevant to add that our determinations date from 1931; it is possible that during this period dietary deficiencies among Negro children were more common or more severe.

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50 mg. of glycerophosphate and 42.4 mg. of sodium diethyl barbiturate (barbital sodium) in aqueous solution. At the end of one hour (or one-half or one-quarter hour, when necessary to avoid hydrolysis of more than about 10 per cent of the substrate) we cool the test tube in ice water, precipitate the proteins with 9 cc. of 10 per cent trichloracetic acid and filter. Phosphatase activity is measured by the difference between the inorganic phosphorus content of this filtrate and the serum inorganic phosphorus. The inorganic phosphorus determinations are performed most accurately by our modification of Kuttner and Lichtenstein's colorimetric method.[8a] The use of serum has further advantage in that serum is sometimes required for calcium determinations, and frequently for inorganic phosphorus and icteric index determinations in the same clinical conditions requiring phosphatase determinations. Jenner and Kay (Plasma Phosphatase: III. A Clinical Method for the Determination of Plasma Phosphatase, Brit. J. Exper. Path. **13**:22 [Feb.] 1932) devised a method requiring three hours' incubation. It yields even lower results, relatively, than Kay's method, probably owing to the employment of glycine as a buffer.

4. Bodansky, A.; Jaffe, H. L., and Chandler, J. P.: Experimental Factors Influencing Blood Phosphatase Values, J. Biol. Chem. **97**:lxvi (July) 1932.

5. Smith, J., and Maizels, M.: The Plasma Phosphatase in Rickets and Scurvy, Arch. Dis. Childhood **7**:149 (June) 1932.

6. Smith, J.: Plasma Phosphatase in Rickets and Other Disorders of Growth, Arch. Dis. Childhood **8**:215 (June) 1933.

7. It seems from the description by Smith and Maizels of their modification of Kay's method that the relatively higher content of glycerophosphate in their substrate would avoid in many cases the errors due to retardation by the products of hydrolysis. The absolute quantities of inorganic phosphorus liberated by both the normal and the pathologic plasma after forty-eight hours' incubation are, however, undoubtedly low.

We have aimed to establish: (*a*) the range of serum phosphatase figures in rickets; (*b*) the value of the serum phosphatase determination as a criterion of the severity of the disease at admission of the patient; (*c*) the value of the serum phosphatase determination as a criterion of healing in rickets, and (*d*) the quantitative relation of the serum phosphatase to the rate of healing. Serum calcium and serum inorganic phosphorus were also determined, and we were able to examine incidentally their value as criteria. As is well known, serum calcium is at present not considered of great importance as a general criterion of severity of rickets.

Our data are summarized in the accompanying table.

*Serum Calcium, Inorganic Phosphorus and Phosphatase in the Course of Treatment of Marked Infantile Rickets**

Date	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Healing†	Treatment
Very Marked Rickets					
Case 1: Female, 4 years					
1931					
4/27	10.3	2.6	...	....	Viosterol (30)
5/13	....	3.5	58	....	
6/ 3	....	5.3	43	....	
Case 2: Female, 3 years					
3/30	8.6	3.3	76	....	None
4/ 7	8.4	2.5	..	....	
4/13	....	...	..	....	Viosterol
4/27	10.2	3.9	37	++	
5/22	10.1	5.0	22	++	
Case 3: Male, 17 months					
1932‡					
2/ 3	9.8	2.7	143	....	Viosterol (60)
2/11	...	3.2	107	....	
2/19	...	4.1	42	+	
2/25	...	4.0	37	....	
3/ 7	9.5	5.7	17	++	
3/23	9.9	5.5	14	....	
4/ 8	10.8	6.2	13	++	
4/20	....	5.9	14	....	Cod liver oil ?
9/28	10.8	4.9	13	....	
1/25	....	5.4	8	....	
Very Marked Rickets					
Case 4: Female, 21 months					
1932					
4/13	9.4	2.7	138	....	Cod liver oil
4/26	....	3.7	135	....	
5/ 9	....	4.6	149	....	
5/12	10.1	4.3	150	+ ?	Viosterol (30)
5/17	....	4.4	139	....	
5/24	....	4.8	140	+	Viosterol (60)
5/31	....	5.9	107	....	
6/ 7	....	5.4	88	....	
6/14	....	4.7	58	....	Cod liver oil
9/ 6	....	4.9	42	....	
Case 5: Male, 2 years					
11/22	6.9	3.8	66	....	Ultraviolet rays, local
12/ 2	...	4.1	75	....	
12/14	9.1	4.0	77	+	
12/20	9.4	4.1	68	+	Ultraviolet rays, general
12/27	...	3.9	59	....	
1/ 4	...	4.4	54	++	
1/13	...	5.3	44	++	Viosterol (60)
1/25	...	5.9	32	+	
2/ 7	...	5.5	20	....	
2/16	...	6.8	22	....	
Marked Rickets					
Case 6: Male, 2 years					
1931					
2/18	9.8	2.3	....	....	None
3/ 6	....	1.5	37.3	....	
3/25	10.2	1.9	55.6	....	Viosterol (60)
4/15	....	...	....	+	Viosterol (90)
4/27	10.6	4.7	15.4	....	
5/12	10.2	5.4	12.6	++	
Case 7: Female, 13 months					
7/14	8.9	2.5	57.0	....	Viosterol ?
8/31	11.2	5.2	....	....	
9/22	....	5.5	7.2	....	
10/13	....	5.6	7.5	....	Cod liver oil ?
2/16	11.8	4.6	10.9	....	
Marked Rickets					
Case 10: Female, 2 years					
1932					
2/25	....	3.1	45.5	....	Viosterol (30)
3/ 7	10.7	5.3	31.3	+	
3/23	11.0	5.8	17.1	....	
4/ 8	10.7	4.8	12.6	++	
Case 11: Female, 21 months					
5/31	8.5	2.5	49.0	....	
6/ 7	....	2.5	57.0	....	Viosterol irreg.
6/22	9.7	3.5	58.0	....	Viosterol (60)
6/28	....	4.5	54.0	....	
7/ 8	....	5.7	27.6	....	
7/21	10.4	5.8	19.0	....	

Serum Calcium, Inorganic Phosphorus and Phosphatase in the Course of Treatment of Marked Infantile Rickets—Continued

Marked Rickets						Marked Rickets					
Date	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Healing	Treatment	Date	Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units	Healing	Treatment
Case 8: Female, 2 years						**Case 12: Male, 21 months**					
7/29	9.1	2.9	51.3	....	Viosterol irreg.	6/18	9.3	3.0	43.8	....	Viosterol (60)
8/19	9.6	5.7	....	....		6/28	...	6.2	40.6	....	Cod liver oil
8/28	10.4	3.8	....	....		9/29	....	5.4	18.2	....	
9/16	9.8	4.0	27.3	....		12/20	...	6.5	17.5	++	
10/ 9	....	6.0	17.5	++		4/13	...	6.0	11.9	....	
Case 9: Male, 2 years						**Case 13: Male, 14 months**					
						6/23	10.0	2.9	51.5	....	Viosterol (60)
10/24	9.8	3.4	31.8	....	Viosterol (60); cod liver oil	7/ 8	....	3.9	32.8	....	
11/ 6	....	3.8	21.3	....		**Case 14: Female, 7 months**					
11/23	10.0	5.5	17.0	++		7/11	....	3.6	49.8	....	Viosterol (30)
11/25	....	...	....	....	Osteotomy; treatment cont'd	7/21	....	5.1	44.6	....	
						7/26	....	7.5	34.3	....	Cod liver oil
12/ 8	10.0	5.2	6.2	....		12/20	10.0	6.6	12.8	....	
						4/12	....	5.7	13.6	....	
Case 15: Male, 5 months						**Case 18: Male, 7 months**					
1932						1932					
12/16	8.6	4.2	36.4	....	Viosterol (60)	2/28	....	4.3	28.0	....	Viosterol (30)
12/20	....	4.7	30.1	....		3/ 7	9.1	4.6	20.6	....	Cod liver oil ?
1/ 4	....	7.9	16.7	+		10/ 3	10.0	5.7	7.1	....	
1/13	....	7.0	14.3	....		**Case 19: Female, 20 months**					
1/25	....	6.8	9.6	++							
2/ 7	9.9	7.1	12.2	....		7/21	10.4	5.9	20.5	....	Viosterol
						7/26	....	5.1	15.9	....	
Case 16: Male, 19 months						8/11	....	4.9	10.5	....	
11/ 7	9.5	3.1	35.1	....		**Case 20: Male, white, 8 months**					
11/ 9	....	3.1	33.5	....		5/ 9	7.3	3.8	29.3	....	Viosterol (30)
11/22	....	4.1	39.7	....	Viosterol (60)	5/17	8.5	4.1	32.2	....	
12/ 2	....	3.6	35.4	+		5/24	....	4.8	26.1	+	
12/14	9.7	3.8	31.7	....		5/27	....	...	....	....	Viosterol (60)
12/27	....	4.2	30.6	++		5/31	10.2	4.8	23.4	....	
1/ 4	....	4.4	14.5	++		6/ 7	9.8	6.1	18.8	....	
1/13	....	5.2	18.5	++		6/14	....	5.0	16.1	....	Cod liver oil
1/25	....	6.1	16.0	++		3/13	10.0	5.3	4.9	....	
2/ 7	....	6.5	15.2	....		**Case 21: Female, white, 14 months (Diabetic "rickets")**					
Case 17: Female, white, 18 months						1933					
1/12	9.8	3.2	14.7	....	Cod liver oil	3/31	11.0	3.4	30.6	....	Diabetic diet
1/27	....	...	....	....	Viosterol and cod liver oil	4/13	....	4.1	24.6	....	
						4/21	....	5.8	17.2	....	
2/ 2	10.4	5.7	10.3	++		5/ 4	....	6.7	11.3	....	
2/19	....	5.0	5.1	....							

* Other analyses were performed but once in a number of patients. These included one patient with marked rickets in whom the serum phosphatase was 62.1 units per hundred cubic centimeters, two children (twins) with very marked rickets and serum phosphatase figures of about 124 and 126 units per hundred cubic centimeters, and one with a serum phosphatase of about 190 units per hundred cubic centimeters.

† The available evidence of healing, from clinical and roentgenologic records, is summarized as follows: +, slow healing; ++, marked and rapid healing. Estimates of the severity of rickets at admission and of the rate of healing while the patients were under treatment were made by Dr. J. Sobel and his staff of the pediatrics service and by Dr. M. Pomeranz, roentgenologist.

‡ In this and other cases, when the observations were carried into the following year, the year can be readily inferred from the other dates stated.

METHODS

Serum inorganic phosphorus and serum phosphatase were determined by methods the details of which have been described,[8] and which represented a

8. (*a*) Bodansky, A.: Phosphatase Studies: I. Determination of Inorganic Phosphate. Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, J. Biol. Chem. **99**:197 (Dec.) 1932; (*b*) footnote 2.

development of procedures similar to those used in our first studies of plasma phosphatase.[9] We noted as a necessary condition for most accurate results that the incubation period in the determination of serum phosphatase be chosen so that hydrolysis of the substrate may not exceed 10 per cent. Greater hydrolysis occurred, however, when initial analyses (after the standard one hour incubation) yielded unexpectedly high values—in excess of 50 units per hundred cubic centimeters—as in marked rickets, polyostotic Paget's disease[10] and experimental jaundice. Numerous tests in which serums of known high phosphatase activity were incubated for periods varying from ten minutes to one hour established the validity of an empirical correction, used but not mentioned in our earlier studies. This correction amounts to 1 per cent for every 10 units (if E represents the uncorrected value in units of phosphatase per hundred cubic centimeters, then $E + E^2/1{,}000$ represents the corrected value). This correction probably applies over the entire range of serum phosphatase values. It is, however, within the limits of error (about 2 per cent) when the value is less than 50 units per hundred cubic centimeters, when the correction is accordingly omitted.

Serum calcium was determined by the Clark-Collip modification of the Kramer-Tisdall method. We had few cases of rickets showing marked hypocalcemia, and calcium determinations were frequently omitted. Analyses were performed, whenever possible, before treatment was begun and at intervals during the period of treatment. Roentgenologic and clinical records were used to verify the evidence of serum phosphatase determinations as to the absence, presence or severity of the rachitic process at admission, and as to the rate of healing under treatment.

Patients were discharged from the hospital for continued treatment at home and for periodic reexamination in the outpatient department. In some cases the treatment at home was irregular, several patients failing to return for periodic reexamination.

RESULTS

Range of Serum Phosphatase in Rickets.—We have already reported the serum phosphatase values which we found in twenty-seven normal children, from 2 to 15 years of age.[10] They ranged between 5 and 13 units, with an average of about 7.3 units. The incidence of the higher values was relatively greater between about 10 and 14 years of age and was possibly related to an increased rate of growth about

9. (*a*) Bodansky, A.; Hallman, L., and Bonoff, R.: Deviation from Beer's Law in the Kuttner-Cohen Method for Determination of Phosphorus, Proc. Soc. Exper. Biol. & Med. **28**:762 (April) 1931. (*b*) Bodansky, A.: Determination of Plasma Phosphatase, ibid. **28**:760 (April) 1931. (*c*) Bodansky, A., and Jaffe, H. L.: Effects of Diet and Fasting on Plasma Phosphatase, ibid. **29**:199 (Nov.) 1931. (*d*) Although Smith and Maizels' and Smith's absolute figures of inorganic phosphorus liberated after forty-eight hours' incubation are low, it is probable that all their results in normal children are subject to errors of about the same magnitude. For that reason we are inclined to accept as valid their evidence of a somewhat higher level of plasma phosphatase in normal children during the first two years, as compared with the older children. Our own series of twenty-seven normal children included only two children of 2 years of age.

10. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: III. Serum Phosphatase in Diseases of the Bone: Interpretation and Significance, Arch. Int. Med. **54**:88 (July) 1934.

this time. Similar serum phosphatase figures were found in a larger group of hospitalized children not suffering from anemia or cachexia, in which the serum phosphatase is lowered, or from bone or liver involvement, in which serum phosphatase is raised. Higher values were indicated in this series for infants of 1 year or younger.[9d]

In twenty-one cases of marked rickets of varying degrees of severity, summarized in the table, which were studied in some detail, and in others which were available for single determinations, serum phosphatase ranged between about 20 units and about 190 units per hundred cubic centimeters.

A distinction between the various criteria of severity of rickets must be mentioned. While the clinical examination takes in a wide range of signs and symptoms, and the roentgenologic examination tells more of the condition of the bone than of the processes taking place within it, the serum phosphatase values in rickets are evidence of processes taking place in bone or bone-forming tissue.[10] Thus, each of these criteria has an independent value, and while a good correlation may be expected in a series of cases, the agreement in any one case need not be perfect. A detailed study of correlation between these various criteria will be published.

Serum Calcium, Inorganic Phosphorus and Phosphatase as Criteria of Severity of Rickets at Admission.—In many cases the severity of the disease had probably been mitigated prior to admission of the patient to the hospital by exposure to the sun, particularly during the summer, even when no other treatment was given. In some cases there was a history of irregular administration of cod liver oil. In general, an estimate of the severity of the rickets at admission permitted the following rough classification on the basis of clinical and roentgenologic records: (*a*) very marked, (*b*) marked, (*c*) mild and (*d*) healed rickets.

Serum calcium at admission was at typically low normal value (about 9.5 mg. per hundred cubic centimeters) in most cases. In two cases (cases 1 and 13) it was normal (about 10 mg. per hundred cubic centimeters) at admission. In case 19, a normal serum calcium at admission, probably due to previous treatment with cod liver oil, was associated with moderately active rickets. In case 6, serum calcium was normal after one month during which no treatment had been received by the patient, although his condition had become aggravated. Marked hypocalcemia was found at admission in only two patients (cases 5 and 20); in several others serum calcium was moderately low (about 8.5 mg. per hundred cubic centimeters). There was no reliable correlation between serum calcium and the severity of rickets in the different cases at admission. For that reason we omitted serum calcium determinations when a sufficient quantity of serum was not available.

Serum inorganic phosphate was generally low in the active cases at admission; when it was not (case 19), there was evidence of previous antirachitic treatment. In the cases with marked hypocalcemia serum phosphorus was generally not as low at admission as in the others, even when there was no history of previous therapy (cases 5 and 20). It was not a reliable criterion of severity of rickets.

The serum phosphatase figures at admission corresponded well with the clinical signs and roentgenologic evidence. We found from 58 to 190 units per hundred cubic centimeters in very marked rickets (cases 1 to 5 and three others not included in the table), from 14.7 to 62 units in marked rickets (19 cases), less than 20 units in mild rickets and normal figures in healed rickets. With the qualification that clinical and roentgenologic judgments of what constitutes these various degrees of severity of rickets are more or less variable, and that there are gradations of severity within each group of cases, we may make the following generalization: More than 60 units of serum phosphatase per hundred cubic centimeters is found in cases of very marked rickets and about 20 to 60 units in marked rickets; in mild rickets the serum phosphatase, about 20 units per hundred cubic centimeters, decreases on a suitable antirachitic regimen; in healed rickets serum phosphatase, which may be about 15 units per hundred cubic centimeters or less, does not decrease on an antirachitic regimen.

Serum phosphatase proved its value as an independent criterion in some cases in which clinical examination indicated active rickets owing to the persistence of clinical signs (enlarged epiphyses, rachitic rosary, etc.), while the serum phosphatase was within the normal range. The diagnosis of healing or healed rickets was obviously indicated and verified by roentgenologic examination.

Serum Calcium, Inorganic Phosphorus and Phosphatase as Criteria of Healing.—Only when the initial serum calcium figures were definitely low was serum calcium markedly affected after treatment; when the initial serum calcium was at the typically low normal or nearly normal level, the quantitative changes after treatment were slight. In cases 3 and 16 serum calcium remained practically stationary, although rapid healing was indicated by the serum inorganic phosphorus and clinical and roentgenologic observations, as well as by the serum phosphatase. In other cases serum calcium rose to 10 mg. per hundred cubic centimeters or higher, sometimes before there was much, if any, other evidence of healing (cases 4 and 6).

Serum inorganic phosphorus responded promptly to treatment, and the rise was definitely graded in any given case in accordance with the size of the dose and the favorable progress of the case. However, normal or even high values (more than 5 mg. per hundred cubic centimeters) were common before healing was far advanced (cases 4, 5, 11, 12, 14 and 19).

The eventual effectiveness of the usual doses of cod liver oil (3 teaspoonfuls daily) or of the smaller doses of viosterol (30 or 45 drops daily) is to be taken for granted in most cases without verification by serum analyses. It is generally desirable, however—particularly when the patient is hospitalized—to establish, on the one hand, whether the rate of healing is sufficiently rapid and to ascertain, on the other hand, the "minimum rapidly effective dose" in each case.

From this standpoint the evidence of serum calcium and even of serum inorganic phosphorus determinations was unreliable, while the rapid and continuing decline of serum phosphatase proved an excellent indication of rapidly effective treatment. In the cases in which the patient was kept under observation sufficiently long the serum phosphatase finally reached normal figures, or became stabilized at or just above a high normal level. This high normal serum phosphatase level seems to be particularly significant. It does not indicate complete healing, although it indicates further progress in the reconstruction of bone than either normal serum calcium or normal serum inorganic phosphorus. Some cases in which we had opportunity for reexamination after the lapse of several months (cases 3, 7, 12, 14, 18 and 20) later showed serum phosphatase figures within normal range. It seems, therefore, that the high normal level at which serum phosphatase is frequently stabilized corresponds to a stage of active reconstruction of bone which may last for several months. When healing is complete, it is indicated by serum phosphatase values nearer the normal average.

Relation of Serum Phosphatase to Rate of Healing.—Perhaps the best indication of the superiority of serum phosphatase as a criterion of effective therapy was its behavior in some cases of active rickets when antirachitic treatment was not given (cases 6, 11 and 16) or was inadequate (cases 4 and 20). Under these circumstances serum phosphatase rose in comparison with the initial figure, revealing the tendency to aggravation of the rachitic process. This tendency is apparently sufficiently strong to overcome early effects of moderate or even rapidly effective doses of viosterol (cases 4, 11, 12, 14 and 16). It is also shown in cases in which discontinuance of treatment resulted in relapse (case 7).

Cod liver oil in doses of about 12 cc. daily was slowly effective in cases of marked or very marked rickets. In such cases it may not produce any effect on the serum phosphatase for a long time (case 4). In less severe cases (case 16) and over a more prolonged period its effects could be demonstrated (cases 12, 14, 17, 18 and 20). In some of these cases of prolonged treatment with cod liver oil the summer exposure to sun may have entered as a factor (cases 4, 12, 14, 18 and 20). Serum phosphatase eventually reached the normal level, with other evidence of healing (case 4 was not available for final determinations).

Viosterol was preferred in a quantitative study of the relation of serum phosphatase to the rate of healing because it is easily administered in doses of graded effectiveness (a 250 D preparation was used).

It was inadvisable to seek to establish, in any one infant, the trend of serum phosphatase at shorter intervals than we have generally used; it was impossible to compare the results obtained in different subjects at various intervals after the first treatment, because many variable factors enter into each case.

The "minimum rapidly effective dose" varied in different children. The procedure by which it was determined was simple. After ineffective antirachitic treatment (cases 4 and 5) or after a control period during which no treatment was given (cases 6, 11 and 16) viosterol was given in doses which were increased to 60 drops daily, and to 90 drops if necessary, until their effectiveness was indicated by a pronounced and continued fall of the serum phosphatase. This indication was supported by other evidence of healing (cases 4, 5, 6, 11 and 16).

A rapidly effective dose of viosterol caused a definite fall of serum phosphatase generally ten days and sometimes as early as four days (case 15) after the beginning of the treatment. Phosphatase figures were stabilized within or near the normal range within about two months.

The stabilization of serum phosphatase at high normal values is more significant than the particular figure at which the serum phosphatase is stabilized. The stabilized value is reached when active healing is in progress but before it is completed, and indicates an adequate dose of antirachitic accessory. It may be well to test the indication by a temporary increase of the dose (unless the inorganic phosphorus is about 6 mg. per hundred cubic centimeters or higher). It is obvious, however, that dietary factors other than the antirachitic accessory are required for the eventual repair of the bone and thus affect its rate. The serum phosphatase determination furnishes a means of checking the effect of the diet as a whole by the rate at which the serum phosphatase declines from the high normal to the strictly normal level.[11]

11. We have discussed elsewhere the biologic significance of serum phosphatase.[10] In rickets the variations of serum phosphatase may be explained as follows: In the absence of vitamin D, normal bone synthesis does not take place. Consequently, the normal controls of the specific reactivity of the bone do not operate, specific reactivity is abnormally high and a high serum phosphatase, as well as excessive production of osteoid, appear among its manifestations. When vitamin D is supplied, the diet being otherwise adequate, synthesis of the bone takes place. Normal synthesis sets up normal controls of specific reactivity, which decreases continuously, the decrease being associated with lower and lower levels of serum phosphatase. During the stage of active reconstruction of the bone specific reactivity is still higher than normal (and is associated with a high normal serum phosphatase), but on completion of repair specific reactivity is finally at the normal level (and serum phosphatase is within the normal range).

A peculiar illustration of the healing of rickets associated with a return to normal serum phosphatase was found in a case of diabetic "rickets" in a child of 14 months (case 21). The initial serum inorganic phosphorus and serum phosphatase were both characteristic of rickets. Diabetic diet for twenty-two days without other treatment brought about definite clinical improvement associated with a rise of serum inorganic phosphorus and a decline of serum phosphatase. Thirteen days later the same tendency continued.

Healed Rickets and Rachitic Deformities.—This group was of no particular interest for continued study. In most of the twenty-five cases the patients had retained some signs of clinical rickets (rachitic rosary, enlarged epiphyses, etc.), and many were deformed. Serum calcium and inorganic phosphorus values were in most cases at the expected normal levels. In three cases the serum calcium was at a low normal, and in six cases the evidence of serum phosphorus alone would have indicated various degrees of rickets (typically low values being found only in two cases). However, the phosphatase figures, which were within the normal range, indicated complete or almost complete healing in the entire group. This indication was confirmed by clinical and roentgenologic records.

COMMENT AND SUMMARY

1. Serum calcium is not a reliable criterion of the severity of rickets at admission or of the rate of healing of rickets.

2. Serum inorganic phosphorus is generally at a low level in severe untreated rickets, and rises on effective treatment. However, serum inorganic phosphorus responds to treatment so quickly that in cases of active rickets with a history of some previous treatment the relatively high serum inorganic phosphorus is not a reliable indication of the severity of the condition at the time of the admission of the patient, nor is it a reliable indication of the stage or extent of healing during treatment.

3. Serum phosphatase, the normal range of which in children may be stated as between 5 and 15 units per hundred cubic centimeters, rises in mild cases of rickets to about 20 or 30 units, in marked cases to about 60 units and in very marked cases above 60 units. These figures, which are supported by clinical and roentgenologic evidence, may be used as criteria of the severity of rickets at admission.

4. The tendency to aggravation of rickets is strong. When antirachitic treatment is not given, serum phosphatase continues to rise; when therapy is not rapidly effective, serum phosphatase may rise at first, then remain stationary or decline to normal values very slowly—over a period of several months. Even when therapy is rapidly effec-

tive, a lag of from four to twelve days may occur before a marked decline of serum phosphatase is observed. This decline continues at a rapid rate until a high normal figure is reached within two months or less. Serum phosphatase may remain at this level for a considerable time while therapy is continued, indicating active repair. However, when complete bone reconstruction has taken place, the serum phosphatase is within the normal range. Serum phosphatase may thus indicate the effect not only of the antirachitic treatment but of the diet as a whole.[11]

5. Determinations of the minimum rapidly effective dose of viosterol or other antirachitic agents by means of serum phosphatase analyses may be of advantage in the treatment of hospitalized patients.

6. Persistence of signs in healed rickets sometimes leads to a diagnosis of active rickets. In those cases a normal serum phosphatase figure may be used to correct the diagnosis. In our experience with this group of cases the evidence of serum phosphatase determinations has been borne out by roentgenologic examinations.

MUMPS MENINGO-ENCEPHALITIS

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DETROIT

Mumps meningo-encephalitis has been recognized as a clinical entity for many years. It is still regarded as a rare condition. The fact that the patients in the seven cases presented here were seen by me in private practice or in consultation during the past six years suggests that the disease occurs more frequently than one has suspected.

For the sake of brevity and clarity, these cases are recorded in a table, on which the following comments are made:

SUMMARY OF CASES

These cases were almost all seen in the first half of the year: two in January, one in March, two in May, one in June and one early in July. The ages varied from 6½ to 10½ years. All but one of the patients were boys. The predominance of male patients has frequently been noted.

The meningeal symptoms coincided with swelling of the parotid glands in one instance. In the other six instances, the former succeeded the latter in from one to seven days. All patients showed some swelling of the parotid glands. Fever, headache and vomiting were noted in all cases, and five of the seven patients were delirious. Convulsions occurred in one instance. Rigidity of the neck, a positive Kernig sign and exaggeration of the deeper reflexes were present in all cases in varying degrees. It will be noted that there was no correlation between these signs and the degree of pleocytosis. Although the signs of meningeal irritation were pronounced in cases 3 and 5, the most moderate degree of pleocytosis was also noted. Neither can any correlation between the severity of symptoms and the degree of pleocytosis be detected. The observations on the spinal fluid are of interest chiefly in that they showed that the extreme predominance of lymphocytes, which is usually present and which has been frequently commented on, is not always found. This fact was also noted by Dopter [1] and Haden.[2] In all these cases, spinal drainage was followed by cessation of vomiting and immediate amelioration of all symptoms. Complete recovery occurred in each case. The patients in cases 3 and 4 were brothers. The latter contracted mumps eighteen days after the onset of his

1. Dopter: Bull. et mém. Soc. méd. d. hôp. de Paris **21**:912 (March 24) 1904.

2. Haden, R. L.: Cerebral Complications of Mumps, Arch. Int. Med. **23**:737 (June) 1919.

Case	Date	Age, Years	Sex	Onset in Relation to Swelling of Salivary Glands: Days After Onset	Onset in Relation to Swelling of Salivary Glands: Coincident With Onset	Involvement of Salivary Glands	Symptoms: Fever	Symptoms: Headache	Symptoms: Vomiting	Symptoms: Delirium	Symptoms: Convulsions	Signs: Ridigity of Neck	Signs: Kernig's	Signs: Reflexes	Observations on Spinal Fluid: Date	Cells: Total	Cells: Polymorphonuclears, %	Cells: Lymphocytes, %	Pressure	Globulin	Sugar	Results
1	7/ 7/27	6½	M	4	..	Both parotids	+	+	++++	0	0	++	++	++	7/ 8	1,700	2	98	+++	+++	..	Complete recovery
2	1/13/30	8	F	1	..	Both parotids	+	++	++	+	0	+	+	+	1/13	90	4	96	+	++	..	Complete recovery
3	5/31/30	8	M	1	..	Both parotids	+	+++	++++	+	0	+++	++++	+++	5/31	27	6	94	+++	+	80	Complete recovery
															6/ 2	105	2	98	++	++		
4	6/24/30	6	M	7	..	Both parotids	+	+++	++++	+	0	++	+++	++	6/24	* 1,140	71	29	+++	++	100	Complete recovery
															6/26	46	33	67	+	+		
5	5/ 9/31	7½	M	5	..	Both parotids	++	+++	++	++	+	+	+++	++	5/ 9	46	5	95	+++	+	77	Complete recovery
6	1/ 4/31	3½	M	..	+	Both parotids	++	+	++++	++	0	++	+	+	1/ 5	477	29	71	++	+++	37	Complete recovery
7	3/18/33	10½	M	6	..	Both parotids	+	++	+++	0	0	+	+	++	3/18	700	42	58	++++	+++	52	Complete recovery

brother's illness. Paddock [3] recorded cases in identical twins, but encountered in the literature no other instance of more than one case in a family. In the cases included in this series there were, in all, five susceptible contacts in whom mumps developed. Case 4 was the only one in which meningo-encephalitis developed.

COMMENT

No extensive review of the literature will be attempted here, since it is already sufficiently voluminous, and has been well reviewed by Acker [4] and Casparis.[5]

Many theories of etiology have been suggested. The following are quoted by Casparis: [5] Eichhorst attributes the symptoms to passive cerebral congestion, dependent on compression of the jugular vein by the swollen parotid; Jaccoud,[6] to emboli from endocarditis; Lannois and Lemoine,[7] to a diffuse meningo-encephalitis, and Gallavardin,[8] to a true meningitis due to the virus of mumps. Casparis [5] was inclined to agree with Gallavardin, but thought it probable that there was an involvement of the encephalon as well as of the meninges. The theory which Casparis attributes to Eichhorst, while too fanciful to warrant serious consideration, is rendered untenable by the occurrence of several well authenticated cases without parotid swelling (Zemke,[9] Howard,[10] Wallgren [11] and Paddock [3]). Jaccoud's theory of emboli from endocarditis seems to have no evidence to support it.

A theory which has received little comment in the American literature is that of Philibert.[12] He considers that the virus of mumps is neurotropic and that the infection is primarily one of the central nervous system. He believes the virus is excreted by the salivary glands and pancreas and may set up a secondary reaction in them, as well as in the testicles and kidneys. This theory is attractive in that it offers an explanation of the cases in which there is no visible swelling of the salivary glands. Against it, however, is the fact that in the majority of recorded cases manifestations of the central nervous system have succeeded the involvement of the salivary glands.

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3. Paddock, B. W.: Mumps Associated with Meningitis in Identical Twins, Am. J. Dis. Child. **44**:565 (Sept.) 1932.

4. Acker, George N.: Parotitis Complicated with Meningitis, Am. J. Dis. Child. **5**:399 (Dec.) 1913.

5. Casparis, H. R.: Cerebral Complications in Mumps, Am. J. Dis. Child. **18**: 187 (Sept.) 1919.

6. Jaccoud: Brit. M. J. **2**:41, 1885.

7. Lannois and Lemoine: Arch. de neurol. **11**:1, 1886.

8. Gallavardin: Gaz. d. hôp. **71**:1329, 1898.

9. Zemke, E. E.: Minnesota Med. **13**:107 (Feb.) 1930.

10. Howard, T.: Am. J. M. Sc. **158**:685 (Nov.) 1919.

11. Wallgren: Acta pædiat. **6**:53, 1926.

12. Philibert, A.: Progrès méd., Jan. 23, 1932, p. 145.

Fatalities have been rare. Maximovitch [13] found edema in the surface of the brain, a semifibrinous exudate in the sulci and hyperemia of the pons and spinal cord. Larkin [14] found an accumulation of slightly turbid fluid in the cisterna magna, congestion of the pia-arachnoid and a grayish-yellow perivascular exudate following the course of the blood vessels. The ventricles were distended with a clear fluid. All cultures were negative. Microscopic sections showed a perivascular infiltration of the pia-arachnoid with large and small mononuclear cells which also extended into the cortex.

In the course of an experimental study of the virus of mumps in 1913, Gordon [15] injected intracerebrally into ten monkeys a Berkefeld filtrate of a gargle specimen from an uncomplicated case of mumps. Four of the monkeys developed symptoms of a nervous disease and died in from three to five days. Sections of the central nervous system showed, in all cases, pronounced degenerative changes in the nerve cells. In one case, one section of the cortex showed definite perivascular infiltration and also foci of leukocytes in the gray matter. Cultures from the spinal fluid and the blood remained sterile. Smears of spinal fluid showed a majority of lymphocytes, but no bacteria.

Opinion as to the frequency with which meningo-encephalitis is encountered during mumps varies widely. In this country the association of the two diseases has been considered a rarity, and variations of opinion are encountered from this extreme to the belief of Philibert,[12] who considers meningo-encephalitis not only a universal companion of mumps, but the primary infection. Several attempts were made to study this point by making systematic examinations of the spinal fluid during mumps. Monod,[16] in 1902, found that six of eight children with mumps showed a definite pleocytosis, although none showed any evidence of meningeal irritation. Nobécourt and Brélet,[17] in 1905, failed to confirm this. De Massary, Tockmann and Luce,[18] in 1917, found a pleocytosis in the majority of forty specimens of spinal fluid from patients with mumps who showed no evidence of meningeal irritation. Haden,[2] however, performed lumbar punctures on a few patients with mumps who had vomited and complained of headache, but showed no other sign of meningitis, with negative results. It seems clear that the incidence of meningo-encephalitis varies with different epidemics of mumps.

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13. Maximovitch, J.: St. Petersb. med. Wchnschr. **5**:185, 1880.
14. Larkin, W. R.: Mil. Surgeon **44**:92, 1919.
15. Gordon, M. H.: Lancet **1**:652 (March 26) 1927.
16. Monod, R.: Réactions méningées chez l'enfant, Thèse de Paris, 1902.
17. Nobécourt and Brélet: Bull. Soc. de pédiat. de Paris **7**:282, 1905.
18. de Massary, Tockmann and Luce: Bull. Acad. de méd., Paris **78**:6, 1917.

The conception of meningo-encephalitis as a complication of mumps is probably erroneous. The infection is apparently due to a virus which has a predilection for the salivary glands, the meninges, the encephalon, the pancreas and the mature gonads. This predilection is apparently strongest for the salivary glands, and they are usually involved, even when there is infection elsewhere. This is not necessarily true, however, as well established cases are on record in which the salivary glands showed no evidence of involvement. This is entirely in line with the general experience with easily demonstrable organisms, such as Bacillus diphtheriae, infection of the middle ears and umbilicus and pneumococcic mastoiditis, meningitis and peritonitis.

The determining factors in the localization of the virus are not clear. From the divergent views as to the frequency with which involvement of the central nervous system occurs, one would conclude that either there is a marked variation in the incidence of mumps meningo-encephalitis, or it has evaded recognition in some localities and in some epidemics. The signs and symptoms are quite definite, and for the most part, unequivocal, so that while it is undoubtedly true that many cases have escaped recognition, it seems reasonable to conclude that wide variation in incidence exists, not only between epidemics, but in different parts of the world. This may be due to some change in the character of the virus itself or to the coincidental presence of some other virus or micro-organism. It is also conceivable that there exist determining factors in the host, dependent on racial, dietary or climatic causes which it is impossible to appraise.

In the present state of knowledge, it seems most reasonable to regard the organs of predilection as the most susceptible points of localization of an infection that is probably primarily a septicemia.

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NEUTRALIZING VALUE OF VARIOUS SUBSTANCES AGAINST LETHAL DOSES

OF (A) STOOL EMULSIONS FROM PATIENTS WITH POLIOMYELITIS AND (B) COLON PARATYPHOID ORGANISMS

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When the serum of patients convalescing from poliomyelitis was injected intraperitoneally into guinea-pigs it protected them from the toxic effects which usually follow the injection of standardized suspensions of stools obtained from patients ill with this disease.[1] I thought that it would be interesting to test other materials.

Several years ago, I received a small amount of antipoliomyelitis serum from Dr. E. C. Rosenow of the Mayo Clinic. When I tested it in 1928 and 1929, I found to my surprise that this serum and a commercial preparation manufactured according to Rosenow's method gave good results, as they prevented the death of many animals receiving injections of toxic doses of stool suspensions. Although of twenty of the protected animals eighteen gave a local cystic response and two an inflammatory response, as compared with seventeen cystic and three inflammatory lesions in the nonprotected animals, only five of the protected group died as compared with fifteen of the nonprotected series (table 1). In like manner, Rosenow's serum gave slight protection against the toxic effect which followed injections of urine from cases of poliomyelitis, eight of the ten unprotected guinea-pigs dying as compared with four of the protected animals (table 2).

In 1928, I decided to test the neutralizing effect of normal horse serum as a negative control experiment. To my surprise, I found that normal horse serum likewise contained definite neutralizing and protective antibodies. Of fifteen animals protected with horse serum, one died, while of fifteen nonprotected animals, nine died (table 3).

The last mentioned experiment was repeated in 1930 with twenty-three animals protected by horse serum and twenty-three controls

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1. Toomey, John A.: Neutralization Experiments in Poliomyelitis: Results of Injections of Stool Emulsions in Animals Previously Passively Immunized with Convalescent Poliomyelitis Serum, J. Prev. Med. **6**:397 (Sept.) 1932.

TABLE 1.—*Neutralizing Effect of Rosenow's Serum Against the Toxic Element Contained in the Stools of Patients with Poliomyelitis* *

Number of Guinea-Pigs Receiving Injections	Injection (2 Days Later)	Died Within				Lesion		
		12 Hours	24 Hours	48 Hours	120 Hours	Inflammatory	Cystic	No Lesion
20 (Previously protected by injections of 5 cc. of Rosenow's serum at various times)	3 cc. of various poliomyelitis stools	5	0	0	..	2	18	0
20 (Unprotected)	Same as above	5	2	6	2	3	17	0

* Method: Two guinea-pigs were used for each experiment. One received an intraperitoneal injection of Rosenow's serum; the other was the control. Two days later, both animals received a subcutaneous injection of 3 cc. of poliomyelitis stool suspension. The dosage of the latter was determined by finding the minimal lethal dose in other animals by trial and error methods.

TABLE 2.—*Neutralizing Effect of Rosenow's Serum Against the Toxic Element Contained in the Urine of Patients with Poliomyelitis*

Number of Guinea-Pigs Receiving Injections	Injection (2 Days Later)	Died Within			Lesion		
		12 Hours	24 Hours	48 Hours	Inflammatory	Cystic	No Lesion
10 (Previously protected by intraperitoneal injections of 5 cc. of Rosenow's serum)	4 cc. urine*	1	1	2	2	8	0
10 (Unprotected)	4 cc. urine*	0	1	7	1	9	0

* This toxic urine was kept on ice two days before it was injected. Rosenow's commercial serum was used in the experiment with the urine.

TABLE 3.—*Neutralizing Effect of Normal Horse Serum Against the Toxic Element Present in the Stools of Patients with Poliomyelitis (1928)* *

Number of Guinea-Pigs Receiving Injections	Injection (2 Days Later)	Died Within			Lesion		
		12 Hours	24 Hours	48 Hours	Inflammatory	Cystic	No Lesion
15 (Previously protected by intraperitoneal injections of 5 cc. of normal horse serum)	3 cc. of poliomyelitis stool emulsion (mildly potent)	0	1	0	10	4	1
15 (Controls)	Same as above	0	2	7	6	9	0

* The method was the same as that described in table 1.

(table 4). The material injected was obtained from the stools of twenty-three different patients. The protection was striking. Nine of the nonprotected and none of the protected animals died. There was a total absence of reaction in fourteen of the protected and in only one of the nonprotected animals, while twenty-two of the nonprotected and nine of the protected animals had indurated and diffuse reactions.

These neutralizing experiments of 1928 and 1930 are interesting in view of the many recent claims of the efficiency of certain anti-poliomyelitis horse serums. One might suggest that horses may have antibodies in their blood serum against the toxic factor present in the stools of patients with infantile paralysis.

TABLE 4.—*Neutralizing Effect of Normal Horse Serum Against the Toxic Element Present in the Stools of Patients with Poliomyelitis (1930)*

Number of Guinea-Pigs Receiving Injections	Injection (2 Days Later)	Died Within			Lesion		
		12 Hours	24 Hours	48 Hours	Inflammatory	Cystic	No Lesion
23 (Previously protected by intraperitoneal injections of 10 cc. of normal horse serum)	3 cc. of poliomyelitis stool* emulsion	0	0	0	9	0	14
23 (Controls)	Same as above	0	0	9	2	20	1

* The stools were standardized by centrifugating 3 cc. of diluted stool in a Hopkins tube so that after five minutes of centrifugation at 2,500 revolutions per minute the reading would be 0.1 cc. in 3 cc. of saline solution. A different stool emulsion was used for each pair of animals (one control and one protected animal). Twenty-three stool emulsions from twenty-three patients with poliomyelitis were tested.

EXPERIMENTS WITH POLIOMYELITIS SERUM

Though I had previously demonstrated the presence of what was thought to be a toxic factor in the stools and urine of patients with poliomyelitis,[2] it might be stated in objection that my results were due to the natural toxicity of the enteric group of organisms or their toxins. Because of this, neutralization experiments were performed against lethal doses of coli paratyphoid organisms with poliomyelitis serums from acutely ill and convalescent patients in an endeavor to parallel as far as possible the experiments in which I used poliomyelitis serums from acutely ill and convalescent patients to neutralize the toxic effect of injections of poliomyelitis stool emulsions.[1] Combina-

2. Toomey, J. A.: Demonstration of a Toxic Factor in the Stools and Urines of Poliomyelitis Patients, J. Prev. Med. **6**:379 (Sept.) 1932.

tions of the coli paratyphoid group in physiologic solutions of sodium chloride were the lethal agents in these experiments.

Method.—The organisms, twenty-three strains in all,[3] were grown on agar, scraped in physiologic solution of sodium chloride and mixed to a dosage that would kill all guinea-pigs weighing 250 Gm. within four days or less following injection. The dosage was usually about 0.1 cc. of bacteria in 3 cc. of physiologic solution of sodium chloride, as standardized in a Hopkins tube by centrifugating the material at half speed (1,000 revolutions per minute) for five minutes.

Ten cubic centimeters of poliomyelitis serum taken from twenty-one acutely ill patients was inactivated, set aside and later injected intraperitoneally into twenty-one guinea-pigs. Ten cubic centimeters of poliomyelitis serum taken from the same twenty-one patients during convalescence was injected intraperitoneally into twenty-one additional guinea-pigs. Another group of twenty-one guinea-pigs of the same lot was set aside as the control group. Two days later, the killing dose of coli paratyphoid suspension was injected subcutaneously in all of the sixty-three animals.

Results.—In Terms of Life and Death: All of the guinea-pigs died, the controls as well as those protected with serums from acutely ill or convalescent patients. There was slight prolongation of life in the group protected by serum from convalescent patients, since only one of the guinea-pigs in that group died within the first forty-eight hours after injection. All of the others in the group, however, eventually died before the sixteenth day—the greatest number (fifteen) before the twelfth day. In the nonprotected control group, eight guinea-pigs died within forty-eight hours after the injection; all of them died before the thirteenth day, and nineteen before the twelfth day. In the group protected by serum from acutely ill patients, five guinea-pigs died before forty-eight hours had elapsed, the remainder within fourteen days and nineteen within twelve days. The only noticeable difference between the groups was the fact that there was a comparative prolongation of life in the animals of the group protected with serum from convalescent patients (table 5).

Gross Pathologic Results: In guinea-pigs which had been given injections of suspensions of stools obtained from patients with poliomyelitis, the local reaction in the subcutaneous area consisted chiefly of a hemorrhagic oozing with marked dilatation of the peritoneal and

3. Eberthella typhi (stock); Salmonella paratyphi A (stock); Salmonella Schottmülleri B (stock); no. 200 S. Schottmülleri (American Type Culture Collection); nos. 207, 208, 209, 745, 845 and 206 Escherichia communior (American Type Culture Collection); no. 26 Esherichia coli (American Type Culture Collection); no. 1 gram-negative bacillus (coli group) from the urine of patients with poliomyelitis; no. 2, from the nose, no. 6, from the throat, no. 7, from the nose, no. 11, from the throat, no. 14, from the nose, no. 28, from the urine, no. 34, from the urine, no. 42, from the urine, no. 62, from the urine, no. 179, from the urine, and M, from the nose and throat of a tuberculous patient in extremis.

cutaneous capillaries. In the animals given injections of coli paratyphoid suspension there was a tendency toward the formation of localized abscesses with limited pyogenic membranes, and oozing was seen only in the guinea-pigs which died within from twenty-four to forty-eight hours after injection. When the intestines were pulled aside, the spleen was observed to be the organ most involved. This was in contrast to the guinea-pigs which received injections of stool suspensions; in these animals the suprarenal glands were the organs always affected.

TABLE 5.—*Neutralizing Effect of Convalescent Poliomyelitis Serum Against Injections of Coli Paratyphoid Organisms*

Group	Number of Guinea-Pigs Receiving Injections	Indurated	Indurated Diffuse	Indurated Cystic	Death Within 48 Hours	Death After 48 Hours
A (Protected with 10 cc. of poliomyelitis serum from acutely ill patients 2 days previous to injection*)	21	5	5	6	5	16 (within period — listed) 3 (6 days) 1 (7 days) 6 (8 days) 1 (9 days) 1 (10 days) 2 (11 days) 1 (13 days) 1 (?)
B (Protected with 10 cc. of poliomyelitis serum from convalescent patients 2 days previous to injection)	21	13	6	1	1	20 (within period — listed) 2 (3 days) 2 (6 days) 1 (7 days) 2 (8 days) 4 (10 days) 4 (11 days) 3 (13 days) 1 (14 days) 1 (16 days)
C (Controls)	21	0	4	9	8	13 (within period — listed) 1 (3 days) 6 (6 days) 2 (7 days) 2 (8 days) 1 (12 days) 1 (13 days)

* The injection in all cases was 3 cc. of saline suspension of organisms standardized in a Hopkins tube to 0.1 cc. of organisms in 3 cc. of saline solution.

Since many guinea-pigs died before forty-eight hours had elapsed, I could divide the animals, protected or unprotected, into two groups: group 1, just referred to, composed of those dying early, and group 2, composed of those dying after forty-eight hours.

In group 1, six guinea-pigs showed grossly and microscopically typical reactions of the suprarenal glands which were similar to, but not the same as, those seen in animals given injections of suspensions of stools obtained from patients with infantile paralysis. Two of these were in the group protected with serum from acutely ill patients, four were controls and none were among the guinea-pigs protected

with serum from convalescent patients (table 6). This in itself was evidence of a slight degree of protection given by serum from patients convalescing from poliomyelitis. According to my former experiments, guinea-pigs which reacted typically to injections of suspension of stools were those which showed a definite cherry-colored or mahogany-colored enlargement of the suprarenal glands.

In group 2 (composed of guinea-pigs dying within forty-eight hours after the injection), fourteen had been protected by serum from acutely ill patients and twenty by serum from convalescent patients; thirteen were unprotected.

Of this group, five animals showed changes in the suprarenal glands as nearly typical as one sees after injections of stool suspensions. I

TABLE 6.—*Time of Death and Appearance of Suprarenal Glands and Spleen*

Major Groups	Minor Groups	Suprarenal Glands		Spleens	
		Typical	Atypical	Enormous	Black
A (Protected with poliomyelitis serum from acutely ill patients, as in table 1)	Group 1, composed of those dying early.....	2	5	2	2
	Group 2, composed of those dying late.....	1	13	7	1
B (Protected with poliomyelitis serum from convalescent patients, as in table 1)	Group 1, composed of those dying early.....	0	1	0	0
	Group 2, composed of those dying late.....	3	17	12	1
C (Controls)	Group 1, composed of those dying early.....	4	4	0	1
	Group 2, composed of those dying late.....	1	12	8	2

say "nearly" because the sinusoidal engorgement was never so marked as it is in suprarenal glands reacting typically after injections of suspensions of stools. One of these five animals with nearly typical changes in the suprarenal glands was in the group protected by injections of serums from acutely ill patients, three were in the group protected by serums from convalescent patients, and one was among the controls. Animals were listed as giving a positive reaction when only one suprarenal gland was involved, although following injections of stool suspension positive reactions were nearly always bilateral.

An obvious difference between the two groups receiving injections was seen when the spleen was studied. The organ was occasionally slightly enlarged and occasionally black in the guinea-pigs which died after injections of stool suspensions. It was nearly always enlarged after injections of coli paratyphoid organisms (sixty-two of sixty-three animals) and at times, enormously so. In twenty-nine animals, it was from twenty to thirty times the size of the normal gland. All except two of the animals with enormous spleens died after forty-eight hours.

Microscopic Examination: Microscopically, the effect of the injections of coli paratyphoid organisms on these animals was noted in the liver, lung, spleen, suprarenal glands and spinal cord. Sections were made of these organs in each guinea-pig which died (sixty-three of the sixty-three receiving injections [table 7]).

There was practically no difference between the spinal cord of the guinea-pigs receiving injections of coli paratyphoid and that of the animals receiving injections of stool suspensions from patients with infantile paralysis; the same lymphocytic infiltration was present in fifty-six of the sixty-three specimens examined, being questionable in five and absent in two.

The spleen was the seat of a definite hypertrophy of the stromatic elements with no obvious hypertrophy of the solitary follicles but with

TABLE 7.—*Microscopic Reactions, According to the Text*

		Suprarenal Glands			Spinal Cords			Spleens			Lungs			Livers		
	Number of Guinea-Pigs	Positive	Negative	Questionable	Positive	Negative	Questionable	Positive	Negative	Questionable	Positive	Negative	Questionable	Positive	Negative	Questionable
A (Protected with serum from acutely ill patients)	21	0	18	3	18	0	3	20	0	1	3	16	2	0	21	0
B (Protected with serum from convalescent patients)	21	1	17	3	19	1	1	21	0	0	0	16	5	0	21	0
C (Controls)	21	2	17	2	19	1	1	21	0	0	0	19	2	0	21	0

a thinning of these follicles and a dispersion of their elements throughout the supporting network of the gland.

In three instances the lungs showed slight focal accumulations of lymphocytes.

The liver was not remarkable, not being dissimilar to the livers of guinea-pigs dying of other acute infections.

The reaction of the suprarenal glands which was seen after injections of suspensions of the stools of patients with poliomyelitis was different from that seen after the injection of coli paratyphoid organisms. In group A, protected by acute poliomyelitis serum, there was no picture of sinusoidal engorgement as seen in suprarenal sections of guinea-pigs into which emulsions of stools from patients with infantile paralysis had been injected. There was often marked hypertrophy of the organ, especially of the cortex, and in three instances a slight increase in the number of red blood cells in the medullary area was seen.

In the group protected with serum from convalescent patients, the gland had, if anything, more cortical hypertrophy. The right gland of

one animal was positive in the sense that it appeared like the glands of the animals receiving injections of infantile paralysis stool emulsions, while the suprarenal glands of three other animals contained a medullary increase in the number of red blood cells. In the control group were two sets of suprarenal glands that could be considered positive and two with an increased number of red blood cells in the medulla.

In short, three (4 per cent) of the animals might be considered to present a microscopic appearance similar to that occurring after injections of poliomyelitis stool emulsion, while eight animals showed an increase in the amount of blood present in the medullary area. Fifty-two (82 per cent) of the sixty-three animals, however, could be classified as microscopically showing a negative suprarenal response.

COMMENT

In the guinea-pigs protected with the serum of patients convalescing from poliomyelitis there was a prolongation of life after injections of coli paratyphoid organisms, but the protection was not enough to prevent ultimate death. This was in direct contrast to the protective reaction given by the serum when stool emulsions were injected. In these cases, convalescent serum injected intraperitoneally prevented the death of animals subsequently given injections of infantile paralysis stool suspensions, while at the same time the majority of the control animals in the same experiment died or gave comparatively a more severe reaction within twenty-four hours after injection.[1]

It might be said that the dosage of coli paratyphoid organisms was a much more severe test of the animal's resistance than the injection of a stool suspension. The number of viable organisms was possibly greater in the group receiving injections of coli paratyphoid suspension, but the animals did not die more quickly. In fact, they died sooner after the injection of infantile paralysis stool emulsion that contained a lesser number of enteric organisms. In contrast, though the animals lived longer and the local reaction was not so severe, serum from convalescent patients protected none of the guinea-pigs receiving injections of coli paratyphoid emulsions, while it was markedly effective in protecting the guinea-pigs which received injections of stool emulsions from the patients with virulent infantile paralysis.

Thus one might speculate that the neutralizing factor in the serum from convalescent patients was not directed solely against the coli paratyphoid organism, and that, if such were the case, there might be two factors involved in the mechanism of the disease: (1) a toxic factor causing initial paralysis of the intestine,[4] the original cause of the disease

4. Toomey, J. A.: The Intestine and Urinary Bladder in Poliomyelitis, Am. J. Dis. Child. **45**:1211 (June) 1933.

being easily neutralized by poliomyelitis serum, and (2) a secondary localized toxic factor caused by the enteric organism present in combination with or independent of the primary factor.

Since the toxic factor of poliomyelitis might be a poisoning of the gray fibers and since it would probably act on gray fibers anywhere, it would be likely to affect the gray fibered sympathetic nerves in organs of ectodermic origin. The medulla of the suprarenal glands should be involved and not the cortex arising from the mesoderm; this is exactly what happens after the injection of suspensions of stools of patients with poliomyelitis.

EXPERIMENTS WITH HORSE SERUM

It is seen that serum from patients convalescing from poliomyelitis was slightly protective when used as a passive immunizing agent against coli paratyphoid organisms, since its injection intraperitoneally into guinea-pigs prolonged their lives when they later received injections of lethal doses of coli mixtures. Although there was no ultimate protection, as all the animals, protected or unprotected, eventually died, the prolongation of life, though brief, was definite.

Horse serum, like serum from patients convalescing from poliomyelitis, efficiently protected animals against the lethal effects of doses of infantile paralysis stool suspensions. Horse serum, like serum from patients convalescing from poliomyelitis, possessed a high agglutinin titer against the coli paratyphoid organisms. I wished, therefore, to test its efficacy as a passive immunizing protective agent in guinea-pigs which would later receive injections of coli paratyphoid mixtures.

Methods and Materials.—The thirty-two animals used were guinea-pigs weighing from 210 to 250 Gm. The lethal injection was 3 cc. of a combined mixture of coli organisms standardized in a Hopkins tube to 0.1 cc. of bacteria for each dose. The organisms were grown on agar for forty-eight hours before they were used. Sixteen of the animals were protected by the intraperitoneal injection of 10 cc. of horse serum. Sixteen were controls. Two days after the passive immunizing dose had been injected, these animals and the controls received subcutaneous injections of the aforementioned dose of coli paratyphoid organisms.

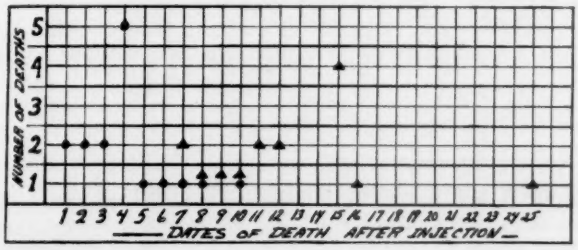
Results.—In the unprotected group, all of the guinea-pigs died, while in the protected group, only one survived. All of the controls, but only five of the protected group, died before the tenth day. The unprotected guinea-pigs began dying within twenty-four hours after receiving injections, and by the seventh day, when the first protected animal died, fourteen of the sixteen unprotected had succumbed. The reaction of different groups is best illustrated by plotting the time of death in the graph.

General Reaction: In most instances, the horse serum prevented a local reaction of a serosanguineous nature. Within twenty-four hours

after local injection into the protected guinea-pigs, there was an inflammatory reaction, sharply localized and in decided contrast to the soggy, indefinite appearance of the abdomen of the unprotected guinea-pigs. Quantitatively, the latter reaction was not at all like the reaction seen after the injection of suspensions of stools of patients ill with poliomyelitis. If the guinea-pigs lived longer than forty-eight hours, the serosanguineous local accumulation changed to pus, with a pyogenic membrane beginning to form about the periphery of the lesion.

Microscopic and Gross Pathologic Examinations: The spleen was always enlarged, but to an enormous extent in six cases. Occasionally the organ was black in both the protected and the nonprotected animals.

The suprarenal glands were only grossly enlarged in one instance, and in only one instance did the medullary area of the gland appear red on section. This was in direct contrast to the reaction seen after the



Graph showing protective action of horse serum against coli paratyphoid suspensions. The dots indicate unprotected animals; the triangles, protected animals.

injection of infantile paralysis stool suspension, when the glands became hypertrophied and varied from mahogany to cherry red, with an obviously angry red medullary area on section.

Microscopic sections of the cord, lungs, liver, suprarenal glands, spleen and kidneys were studied.

The cord showed the same lymphocytic infiltration and destruction of nerve cells throughout the sections that appeared in previous sections of animals which had received injections of infantile paralysis stool suspensions.

In all of the pulmonary specimens examined there was slightly more than the average amount of oozing, and the specimens themselves were splotchy in four instances. Microscopically, slight hemorrhage was present, and in the lobes of four lungs there were focal accumulations of lymphocytes.

The liver was friable and the seat of cloudy swelling. There was nothing, however, that could distinguish these organs from those obtained from animals dying of any other acute infection.

The suprarenal glands were small in all but one instance in which the gland was markedly hypertrophied. This hypertrophied gland seemed to show a positive reaction on cut section, though most of the hypertrophy was in the cortical area. When examined microscopically, there were extra filled sinusoids in the medullary area, but the medullary tissue could still be recognized. In another instance, there was a slight increase of red cells in the medulla. All other cut specimens were negative for the sinusoidal engorgement that appeared in the glands of animals that died after injections of infantile paralysis stool suspensions.

The spleen was enlarged in every instance, sometimes enormously so, but not to the extent seen in the experiments in which convalescent serum was used to protect the animals against the lethal effects of coli paratyphoid suspension. Here, as in the experiments just referred to, the microscopic splenic picture was the same. The normally engorged and well contained vessels, central and otherwise, were not present, and the gland was hypertrophied in its stromatic elements. There was a rather even dispersion of the cells of lymphoid follicles into the tissue, but so far as I could determine there was no increase in the number of follicles.

COMMENT

In the foregoing experiment, we found that horse serum protected guinea-pigs to a slight extent against the effect of injections of coli paratyphoid organisms, since the lives of guinea-pigs given the serum were prolonged.

The suprarenal glands were not involved as were the suprarenal glands of the guinea-pigs which received injections of stool suspensions from patients with poliomyelitis. On the other hand, the spleen was always enlarged.

Horse serum and poliomyelitis serum from convalescent patients protected guinea-pigs that received injections of lethal doses of poliomyelitis stool emulsions. The serum gave only slight protection against injections of lethal doses of coli paratyphoid organisms. It is not proved, but it might be suggested, that besides the organisms there was an additional noxious factor—a toxin—present in the stools of patients with poliomyelitis, since horse serum and serum from patients convalescing from poliomyelitis were able to neutralize the immediately more toxic poliomyelitis stool emulsions, while they were not able to protect any of the animals which had received injections of combinations of live coli paratyphoid organisms.

CONCLUSION

1. Serum obtained from Dr. Rosenow as well as commercial serum manufactured according to his method contained neutralizing bodies against the toxic factors present in the stools and urines of patients with

poliomyelitis. Normal horse serum, however, was equally good when used as a neutralizing agent against the same toxic factors present in the stools of patients with poliomyelitis.

2. Serum from patients convalescing from poliomyelitis when injected intraperitoneally into guinea-pigs prolonged the life of the animals if they subsequently received injections of suspensions of coli paratyphoid organisms. In the dosage used, it did not prevent the ultimate death of the animal.

3. The pathologic reaction of the cord was the same after injections of coli paratyphoid organisms as it was after injections of infantile paralysis stool emulsions.

4. The spleen, and not the suprarenal glands, was the organ most involved after injections of coli paratyphoid organisms.

5. Horse serum when injected intraperitoneally into guinea-pigs prolonged the lives of the animals that later received injections of lethal doses of coli paratyphoid suspensions. Unlike the animals which received injections of stool emulsions from patients with poliomyelitis, the pathologic reaction was most obvious in the spleen.

REFLEX CHANGES IN TYPHOID FEVER

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One of the earliest neurologic changes in poliomyelitis is a modification of the abdominal cutaneous reflex.[1] In frank cases of paralysis of the abdominal musculature, this lack of reflex response may be due to a lesion of a lower motor neuron of the somatic system—a break in the motor arm of the reflex arc. Usually, however, in poliomyelitis, the abdominal rectus muscles are not paralyzed even though the reflex may be lost. In other neurologic diseases manifesting a loss of abdominal reflexes, it is usually said that this loss of reflex response is the result of an irritation of the upper motor neuron, because of which reflexes acquired later in ontogeny disappear, and more primitive responses become more obvious. Some of these theories are discussed in a previous article.[1]

Since I believe that poliomyelitis has its origin in, or at least its spread from, the gastro-intestinal tract, I decided to make a clinical study of the reflexes in another disease that was frankly gastro-intestinal in origin, namely, typhoid fever.

The election of this disease for reflex study was not inappropriate for two reasons: 1. It had long been known that persons with this infection may actually go into what Osler [2] called a "state of poliomyelitis." 2. It was shown long ago that one of the most common neurologic changes accompanying this infection was the loss of the abdominal reflex.

Rolleston [3] studied the abdominal reflex response in forty-five cases of enteric fever and attributed considerable diagnostic and prognostic importance to this reaction. He concluded that no constant relationship existed between the loss of the abdominal reflex and the condition of the tendon reflexes. In fifteen of his patients ankle clonus developed, and four had positive Babinski responses. Nothing was mentioned of the sequence of reflex disturbance in individual patients. It was, therefore, thought advisable to study this factor.

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1. Toomey, John A.: Some Reflex Changes in Poliomyelitis, Am. J. Dis. Child. **46**:730 (Oct.) 1933.

2. Osler, William, and McCrae, Thomas: Principles and Practices of Medicine, ed. 11, New York, D. Appleton & Company, 1930.

3. Rolleston, J. D.: The Abdominal Reflex in Enteric Fever, Brain **29**:99, 1906.

Thirty-one cases of typhoid fever were seen during 1930 and 1931 in the City Hospital and in other places in Cleveland. The only conclusion that could be drawn from the disconnected data obtained from the histories and neurologic examinations was that the abdominal reflex was frequently lost. Most of these patients were not seen until the illness had lasted about three weeks, since the diagnosis was not made at the onset, and the case was not reported to the Board of Health as typhoid fever until the Widal reaction had become positive. By that time, all of the neurologic reactions had either established themselves or had returned to normal, so that reliable information as to the sequence of their occurrence could not be obtained.

It was decided to study only the cases in which the actual length of the period from the time of exposure to the advent of symptoms was known, i. e., cases which could be studied during the entire course of the disease. Obviously, this meant that many cases of typhoid fever would be ignored since they were seen late in the course of the disease and at a time when neurologic reflex reactions had become established.

In 1932, I had the opportunity to study five small epidemics of two or three cases each. In all, there were thirteen cases; eight of the patients were admitted to the contagious division of the City Hospital in the earliest stages of the infection. Though this number may seem small, it is large when one considers the critical criterion under which it was decided to work. Nearly all these cases occurred in persons exposed to the disease who came from families in which known cases of typhoid fever occurred; the dates of onset, symptoms and exposure were definitely known.

The plan in this study was to follow the clinical progression of the disease, to determine when after the onset of the infection the changes in the reflexes occurred and then to note the time interval or the synchronicity of occurrence of the reflexes with each other. The reflexes studied were the abdominal cutaneous reflex, the knee jerk, the ankle clonus and the Babinski sign.

To summarize the results, the severity of changes in the reflexes and the length of time they were present roughly paralleled the severity of the infection. The patients usually had a period in which they had no complaints save for malaise and fever. From seven to ten days after the onset of the disease the abdominal reflexes were modified, a modification usually evinced by a complete absence of response to stimulation, if not in all, at least in the infra-umbilical quadrants. This type of reaction occurred even though the abdominal rectus muscles could be voluntarily activated with ease. Within from twenty-four to seventy-two hours later the knee jerks became hyperactive in eleven cases and hypo-active in one case. The knee jerk response was followed two or three days later by the appearance of a pseudo and then

of a sustained ankle clonus. Finally, again in a day or two, a Babinski reflex appeared, though this plantar response was not present in every instance (table).

It became obvious that the important point about these neurologic reflex responses was the orderly sequence of the changes: (1) the loss of the abdominal cutaneous response; (2) the onset of hyperactive knee jerk responses to stimuli; (3) the appearance of ankle clonus, and

*Time and Sequence of Changes in Reflexes after the Onset of Typhoid Fever in Thirteen Cases**

Abdominal Reflexes	Knee Jerks	Ankle Clonus	Babinski Reflex
12 cases showed loss of reflexes in from 7 to 15 days	11 cases showed hyperactive responses in from 8 to 17 days	10 cases showed bilateral sustained ankle clonus in from 10 to 19 days	3 cases showed Babinski reactions in from 12 to 40 days

* One mild case showed no neurologic disturbances.

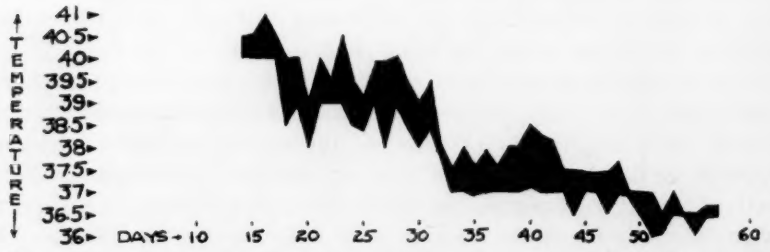

Fig. 1.—Temperature readings in a patient with severe typhoid fever which developed after a known exposure. Typhoid vaccine was given on the day after the patient had drunk infected well water. On the fourth day after exposure there was headache; on the sixth, diarrhea; on the eighth, the patient was examined at home; all the reflexes were present, and there was fever; on the fourteenth day the patient was admitted to the hospital; the white cell count was 5,775; the spleen was palpable; on the fifteenth day the abdominal reflexes were absent; on the sixteenth day the patient was delirious; on the seventeenth day the Widal test (1:160) showed an overflow of agglutinins for paratyphoid A and B; the knee jerks were hyperactive. On the nineteenth day the quadriceps femoris reacted to a galvanic current of 40 volts; the ankle clonus was present; on the twenty-first day the Babinski reflex was present. On the twenty-seventh day the quadriceps femoris reacted to a galvanic current of 50 volts; on the forty-first, it reacted to a galvanic current of 55 volts. On the forty-third day the abdominal reflexes were present. On the forty-sixth day the quadriceps femoris reacted to a galvanic current of 55 volts. On the forty-eighth day the pathologic reflexes had disappeared, and on the fifty-seventh day the quadriceps femoris reacted to a galvanic current of 45 volts. The curves in this and in the succeeding charts begin with the patient's admission to the hospital. The upper and lower points of the shaded portions represent the highest and lowest temperature readings for that particular day.

(4) the establishment of a Babinski reaction. As stated, not all the cases progressed to the last mentioned stage. If the disease was severe and the quadriceps muscle exceptionally weak, the knee jerks occasionally later became hypo-active.

All the patients recovered. The first reflex to become normal was the abdominal reflex response. When this had occurred, the patient was always subjectively better; the bowels became normal again, and anorexia disappeared. The other reflex reactions became normal at varied lengths of time after the abdominal reflex response had returned to normal. The usual sequence was that after the abdominal response became normal, the knee jerk became less active to stimuli and then the pathologic reflexes disappeared. In one case the abdominal reflex response disappeared again with the onset of a relapse.

Coincident with the early hyperactivity of the knee jerk, weakness of some of the somatic muscles of the thigh occurred, and in time this

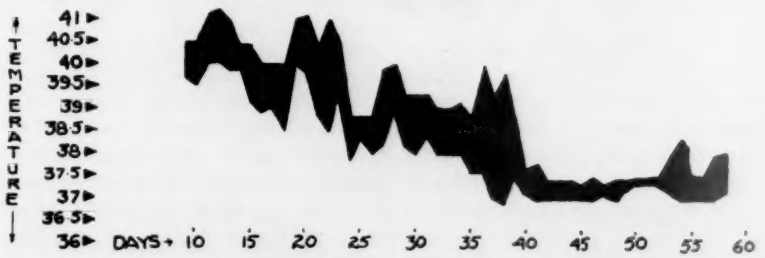

Fig. 2.—On the second day of the disease the patient was examined at home; all the reflexes were present. On the fourth day diarrhea appeared. On the ninth day the patient was admitted to the hospital. On the tenth day rose spots appeared; the spleen was palpable. On the eleventh day a culture of the stool was positive; the white cell count was 6,100; the quadriceps femoris reacted to a galvanic current of 40 volts. On the twelfth day a blood culture was positive; the abdominal reflexes had disappeared. On the fourteenth day the knee jerks were hyperactive; on the fifteenth, the ankle clonus was present (unsustained); the cremasteric reflex was normal; on the seventeenth, the ankle clonus was sustained on one side. On the eighteenth day the patient was delirious; on the twentieth, there was bilateral sustained ankle clonus; on the twenty-first, the quadriceps femoris reacted to a galvanic current of 50 volts; on the thirty-second, it reacted to a galvanic current of 65 volts. On the thirty-third day the Widal reaction was positive (1:80); on the thirty-sixth, the ankle clonus was present; the knee jerks were hyperactive, and the abdominal reflexes, normal. On the fortieth day the Babinski reflex was present; on the forty-third day there was fecal impaction. On the forty-fourth day an atypical plantar response, and on the forty-fifth, unsustained clonus appeared. On the forty-sixth day the quadriceps femoris reacted to a galvanic current of 55 volts. On the fiftieth day the Babinski response was absent, and on the fifty-fourth, the reflexes were normal. On the fifty-seventh day the quadriceps femoris reacted to a galvanic current of 50 volts. On the eighty-eighth day the patient returned to the hospital. The quadriceps femoris reacted to a galvanic current of 35 volts.

weakness gradually became more marked. This decrease in the strength of the muscles with an increase in reflex response is unusual in lesions of an upper motor neuron. Even when ankle clonus developed later, there was no true spasticity. A definite weakness of the extremities was found even though all the neurologic reflex evidences of a lesion of an upper motor neuron were present. A similar condition minus the Babinski reaction occurs in early poliomyelitis, a weakness which has been likened to the effect which follows sections of lumbar sym-

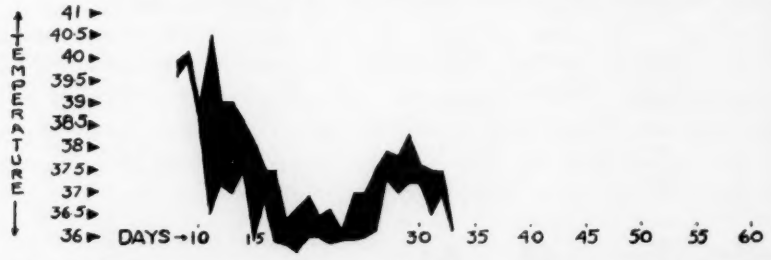

Fig. 3.—Mild type of typhoid fever with little or no symptoms, no neurologic reactions and quick recovery. Compare the clinical course in this case with that shown in figure 4, for the son of this patient. On the second day of the disease the patient was examined at home; all the reflexes were present; on the third to the fourth day diarrhea and fever, and from the fifth to the eighth, abdominal cramps appeared. On the eighth day the patient was admitted to the hospital. On the ninth day rose spots appeared; the white cell count was 3,000; the spleen was palpable. A positive Widal reaction (1:80) was obtained on the fifteenth day and a positive culture of the urine on the sixteenth.

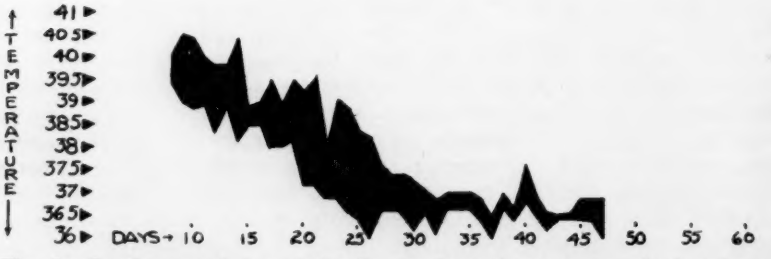

Fig. 4.—On the second day of the disease the patient was examined at home; all the reflexes were present. On the third day there was malaise and on the seventh, nosebleed. On the eighth day fever appeared; the patient was admitted to the hospital; on the ninth day the blood culture was positive; the white cell count was 3,750; the spleen was palpable. On the tenth day the upper abdominal responses were absent. On the twelfth, the quadriceps femoris reacted to a galvanic current of 30 volts. On the thirteenth day rose spots appeared; the abdominal reflexes were absent. On the fifteenth, the quadriceps femoris reacted to a galvanic current of 38 volts. On the sixteenth day the abdominal reflexes were present and normal, and on the seventeenth, the quadriceps femoris reacted to a galvanic current of 30 volts. On the eighteenth day the Widal reaction (1:80) was positive.

pathetic nerves.[1] Curiously enough, in typhoid fever this weakness is not found to the same relative degree in any of the groups of muscles in the arm.

Because of this weakness in the muscles of the leg, studies were made on the response of the various groups of muscles to galvanic stimulation. This was done with a galvanic current generated by a McIntosh wall type of instrument. The "make" and "break" were made through a push button operated by hand. As the disease progressed, it was found that the groups of muscles of the lower extremities showed a definite decrease in their response to galvanic stimulation; this decrease roughly paralleled the increase in neurologic reactions. More voltage was needed to contract the groups of muscles of the leg, and a greater latent interval occurred between the stimulation and the response.

By comparison, the reaction of the muscles of the arm to a galvanic current was normal.

In the upper extremity, Mayer's and Hoffmann's signs (digital reflex response) were never pathologic; the deep tendon reflexes were not unduly hyperactive, and cloni of any part of the limb could not be elicited. In short, the lower extremities showed a response typical of a lesion of an upper motor neuron so far as the reflexes were concerned, with weakness rather than spasticity of the muscles, while the arms evinced no hyperactivity, no pathologic reflexes and no marked muscular weakness. These facts suggested that the effect of the toxic irritant was localized at least below the cervical enlargement and probably in the lumbar area. The cremasteric reflex, a real spinal arc reflex, was present in all but one of the male patients.

COMMENT

In severe cases of typhoid fever there is a disease of the gastrointestinal tract with general symptoms of toxemia, local neurologic signs and reactions in most instances well defined to the lower half of the body. Long ago Siccard [4] thought that the reflex changes could be explained as an extension of the poison of the disease to the sympathetic system.

The mechanism of the neurologic reflex reactions is easily explained on an anatomic basis. The toxins of Bacillus typhosus could be absorbed along the gray fibers of the sympathetic nerves so that the postganglionic fibers would be involved, with a resulting modification of the abdominal reflexes. The reverse of MacKenzie's visceromotor reaction following stimulation would then occur. If further absorption could be conceived as traversing the gray fibers until it reaches the somatic, irritation of the somatic nerve would ensue with a heightened response

4. Siccard, quoted by Rolleston.[5]

of the knee jerk to stimulation. Sustained irritation could give rise to hyperirritability and cloni. The effect of toxin usually ends there. It could, however, spread to the cell of origin of the sympathetic fibers, posterior to the lateral pyramidal tract column, especially if absorption is along the sympathetic sensory fibers. There its very position in the lateral cord area would tend to irritate the contiguous cell column of the pyramidal pathway, and a Babinski response would be the result. The early disproportion between the pulse rate and the temperature has often been explained on the basis of irritation of the peripheral vagus nerve.

Not all patients who contract typhoid fever react in the same way. Some may have diarrhea and only an ephemeral intestinal stasis. Conse-

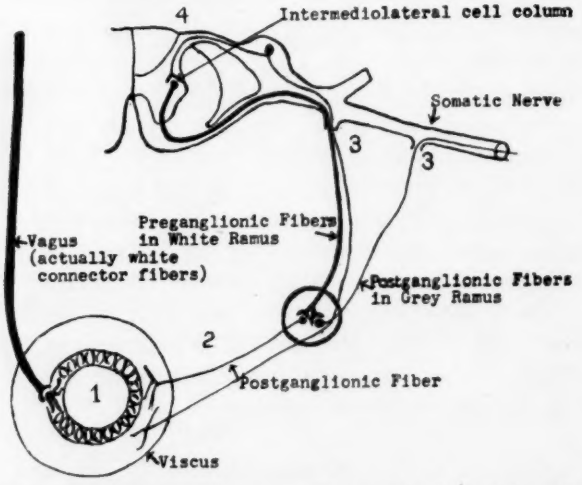

Fig. 5.—Schematic drawing giving a possible explanation of the reflex responses in typhoid fever (slightly modified from the original by S. W. Ranson [Ann. Int. Med. **6**:1014, 1933]). At *1* there is formation of typhoid toxin, an irritant. This is evidenced by the vagus response with bradycardia. It is assumed that at the stage represented by *2* paralysis of the small intestine occurs as well as a spread of the poison along the postganglionic fibers and intestinal sympathetic sensory nerves; this is evidenced by a loss of the abdominal reflexes. At *3*, the toxin spreads toward the somatic nerve, reaches it and irritates it, and hyperactive reflexes may result. At *4*, the toxin may spread along the sympathetic fiber to the cell of origin of the connector and sensory fibers in the intermediolateral cell column. Because of the contiguity of the latter with the pyramidal tract, a temporary Babinski response may ensue from local irritation.

quently, there is no marked neurologic response, or if such a response is present, it lasts only for a short time. Likewise, it is probable that ambulatory or abortive types would show no neurologic abnormalties. Nearly all the patients observed were severely ill and at one time or another had lost the abdominal reflex response.

One could argue that the lesion is still primarily due to an irritation of the lateral pyramidal tract and that the subsequent observations are what one would find in a toxic irritation of an upper motor neuron. If this were to be admitted, however, it would be difficult to explain satisfactorily why all the signs of a lesion of an upper motor neuron still persist when the patient has recovered and when the abdominal reflexes have returned to normal. This is a dilemma that could easily be solved if one were to accept an anatomic basis for these disturbances of reflex reaction.

A chart is presented which gives a possible explanation of the reflex response in typhoid fever (fig. 5).

CONCLUSIONS

1. The earliest neurologic response in the severe cases of typhoid fever studied was a loss of the abdominal cutaneous reflex response. Later, at varied intervals during the course of the disease, the knee jerks became hyperactive, the ankle clonus was obtained and the Babinski reaction appeared.

2. For diagnostic and prognostic purposes it is important to study the sequence of occurrence of these reactions.

3. An anatomic explanation is suggested.[6]

6. Twenty-three cases were seen during the summer of 1933, six of which were studied from the onset of the disease, the findings being similar to those obtained in 1932.

ROENTGEN EXAMINATION OF PYLORIC CANAL OF INFANTS WITH CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

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In a former article,[1] we demonstrated the importance of roentgen examination, following a definite scheme, when there is a question of congenital hypertrophic stenosis of the pylorus. The purpose is to demonstrate the pyloric canal in its longest dimension, which in normal children averages only from 1 to 2 mm.

In order to determine the proper treatment it is also necessary to ascertain the retention of barium sulphate in the stomach. As retention can be entirely absent in one roentgen examination, in the presence of serious hypertrophy of the muscle, it is sometimes necessary to repeat the examination. In a recent publication Voss [2] came to the same conclusion. Moreover, he pointed out the sharply marked outline of the pyloric canal in respect to the stomach and the bulbus duodeni. Peristalsis of the pyloric canal is absent, and the bulbus unfolds itself insufficiently. Voss took little account of the peristalsis of the stomach and spasms of the musculature of the esophagus; he considered the possible retention in the stomach of little value.

Our opinion [1] was that the trouble is entirely due to spasm of the muscle, whether hypertrophic or not.

To prove our assertion we stated our experience with one patient; at the first roentgen examination the contents of the stomach passed immediately, while at another examination they were retained for two hours. Moreover, we noticed several times that when the examination was begun, the stomach contents passed quickly into the duodenum and the pylorus was then closed for a considerable time.

The clinical picture of the case has a certain value, as it necessitates a roentgen examination that will give certainty. Moreover, it indicates

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1. Meuwissen, T., and Slooff, J.: De röntgenologische herkenning van de congenitale hypertrophische pylorus-stenose, Maandschr. v. kindergeneesk. **1**:107, 1931.

2. Vose, E. A.: Röntgenuntersuchung der hypertrophischen Pylorus-Stenose, Ztschr. f. Kinderh. **53**:650, 1932.

the treatment that one has to follow. The degree of emaciation and the stubbornness and quantity of the vomit indicate the degree of stenosis and whether an operation is necessary or not. This conclusion, however, is correct only if the film shows distinct hypertrophy of the muscle. Unreliable to some extent are the clinical symptoms: "hypertonic appearance," peristalsis of the stomach and more or less violent vomiting. We pointed out a case in which all the symptoms were present but there was no stenosis. The operation showed no sign of hypertrophy of the pyloric muscle. Sometime afterward a roentgen examination showed (the clinical picture persisting) that the barium meal left the stomach immediately. An observation of Sauer [3] proves that with severe hypertrophic pyloric stenosis peristalsis may be absent. One of our patients, with decided hypertrophy of the pylorus according to roentgen examination, suddenly stopped vomiting though peristalsis and long retention of the stomach contents continued.

In the following case reports we record our observations on different degrees of hypertrophy of the pylorus and the symptoms thereof. The technic followed in this examination is the same as that described in our previous article. Fluoroscopy is important, as it indicates the location of the pylorus and its behavior. A series of from six to twelve films complements the fluoroscopy; only a few of the films can be reproduced here.

REPORT OF CASES

Case 1 shows that vomiting may be absent even with rather severe pyloric hypertrophy, although the distended stomach and retention of the barium meal pointed out distinctly the presence of stenosis.

Case 1.—Arnold B., aged 3½ months, was admitted to the hospital on May 16, 1932. His weight was 6,000 Gm. He had been exclusively breast fed and had vomited only once, about a month before admission. One day the mother noticed strong peristalsis in the stomach region, a symptom of which she knew the meaning only too well, as a brother of the patient was operated on in our hospital for pyloric stenosis on Sept. 30, 1930, a hypertrophic muscle being evident.

The patient was apparently healthy and quiet. He showed rather typical peristalsis but did not vomit.

On May 18 roentgen examination was made, and 22 cc. of fluid, containing no hydrochloric acid, was taken from an empty stomach. After the ingestion of two teaspoonfuls of a barium sulphate suspension, the film showed a long but wide pyloric canal.

Twenty cubic centimeters of barium sulphate was given; half an hour later a small quantity of it had passed the pylorus; the duodenum was filled with it. The long pyloric canal (11 mm.) was now very narrow, as figure 2*A* shows. After two and one-half hours, about one half of the barium meal was retained in the stomach. Breast feeding thereafter did not give rise to peristalsis.

3. Sauer, L.: A Further Contribution to the Study of Pyloric Stenosis, Am. J. Dis. Child. **22**:166 (Aug.) 1921.

I shall now report a group of seven cases in which the pyloric canal as measured on the film was from 16.5 to 24 mm. long and in all of which operation was performed.

CASE 2.—Nico B., aged 5½ weeks, was admitted to the hospital on Jan. 21, 1932. His weight was 4,400 Gm. He had vomited with moderate force sometimes before and sometimes after nursing, ever since the seventeenth day after birth. We noticed strong peristalsis of the stomach. The baby vomited a great deal, but only once was there a little blood with the vomit.

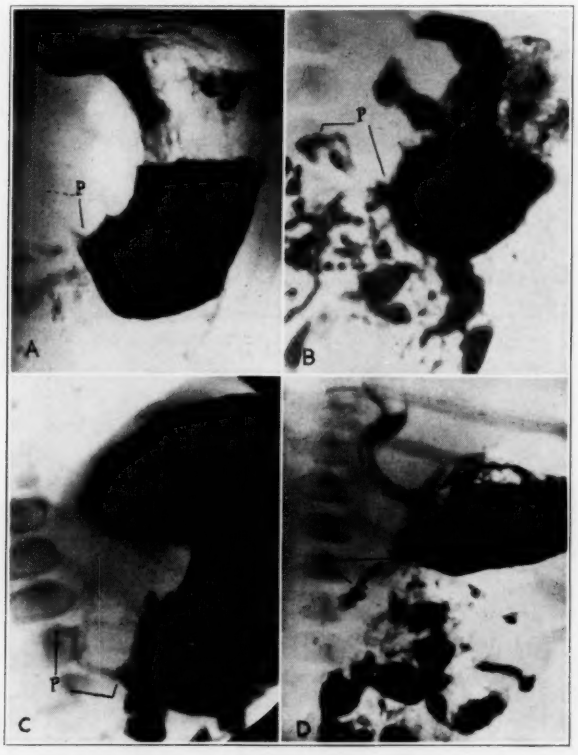

Fig. 1.—*A* shows failure of the pyloric canal to fill in case 2. *B* shows the canal in case 3, 24 mm. long; *C*, that in case 4, 21 mm. long, and *D*, that in case 8, 16.5 mm. long.

Roentgen examination was made on January 25. From the empty stomach 50 cc. of colorless fluid was removed (free hydrochloric acid, 5; total acid, 46). After six hours the barium meal was still in the stomach; nothing had passed into the intestines. The pyloric canal did not fill at all. There was quite an amount of fluid on top of the barium.

A second roentgen examination was made on January 26. Three hours previously the patient was given 40 cc. of barium suspension. It was now possible to force a little of it through the pyloric canal. This appeared to be very narrow, but its length, although abnormal, could not be determined (fig. 1*A*). The adja-

cent stomach shadow showed a depression. At the time of the operation this was explained as being due to the fact that the pyloric muscle was pushed inward like a portico.

On January 27, the patient was operated on by Dr. Verbeek. The stomach was very much distended. There was severe hypertrophy of the pylorus, the most severe that we have witnessed. An hour after the operation the incision still bled; the abdominal cavity contained some blood; there were no bleeding vessels. Examination of the blood showed: 3,000,000 erythrocytes per cubic millimeter, 300,000 platelets, and calcium, 12 mg. per hundred cubic centimeters—a normal picture.

A transfusion of 90 cc. of blood was given, after which the hemorrhage ceased.

On January 28 there was severe vomiting.

On January 29 the patient had another hemorrhage during the night. The coagulation time of the blood was normal. A transfusion of 100 cc. of blood stopped the bleeding.

Following the operation the patient vomited only now and then. On February 9 the vomiting had stopped, and the patient was discharged. No explanation can be given for the hemorrhages.

CASE 3.—Cornelius K., aged 4 weeks, was admitted to the hospital on Jan. 2, 1933. His weight was 3,200 Gm. He had been exclusively breast fed. He had vomited violently and copiously during or after nursing ever since the fifth day of life. While he was nursing we noticed strong peristalsis in the stomach region.

Roentgen examination was made on January 3. No secretion was obtained from the empty stomach. The film showed an extremely long pyloric canal (24 mm.). The barium suspension had penetrated the folds of the mucous membrane (fig. 1 *B*). After four hours, two thirds of the barium meal was retained.

On January 4, the patient was operated on by Dr. Verbeek. The wall of the stomach was very thick. The pylorus was hypertrophic; the muscle was 21 mm. long.

On January 18, roentgen examination was again made. No secretion was obtained from the empty stomach. The pyloric canal was still very long and narrow; after three hours the stomach was empty.

CASE 4.—Marlise Sch., aged 7 weeks, was admitted to the hospital on June 20, 1933. Her weight was 2,200 Gm. She had vomited a great deal after every feeding whether by breast or by bottle since the fourth day after birth. While she was nursing we noticed strong peristalsis of the intestines all through the abdomen, followed by typical peristalsis of the stomach. After ingesting from 40 to 50 cc., the child gushed forth great quantities of curdled milk.

On June 21 roentgen examination was made. No secretion was obtained from the empty stomach. The pyloric canal ran in an anteroposterior direction; it was very narrow and 21 mm. long. Figure 1 *C* shows distinctly the folds of the mucous membrane converging toward the pyloric canal (Engel [4]). After three hours the stomach retained four fifths of the barium meal.

On June 22 the patient was operated on by Dr. Verbeek. The pyloric muscle, 19 mm. long, was cut. Vomiting continued for a few days rather violently and then stopped.

CASE 5.—Jozef V., aged 6 weeks, was admitted to the hospital on May 31, 1932. His weight was 3,650 Gm. He had vomited violently before and after

4. Engel, S.: Die Bedeutung der Schleimhaut für das Zustandekommen und die Behandlung der spastischen Pylorusstenose des Säuglings, Kinderärztl. Praxis **3**:49 (Feb.) 1932.

artificial feeding since the fourth day after birth. There was strong peristalsis of the stomach.

On June 1 roentgen examination was made. From 2 to 3 cc. of secretion was obtained from the empty stomach. The stomach was enlarged. Twenty cubic centimeters of barium suspension was given. A little passed immediately through the pyloric canal, which was 19 mm. long, and then for three hours none passed.

On June 3 the patient was operated on by Dr. Verbeek; the pylorus muscle, 18 mm. long, was cut.

The patient vomited only once after the operation. He was discharged on June 18.

Case 6.—Frits K., aged 5½ weeks, was admitted to the hospital on Sept. 16, 1931. His weight was 3,950 Gm. He vomited the first week after birth and then stopped vomiting. Violent vomiting began again seven days before admission before and after exclusive breast feeding. The vomitus was yellow. While the patient was nursing we noticed first tonic spasm and afterward strong peristalsis in the stomach region. The peristaltic waves advanced until about 3 cm. to the right of the umbilicus, when hiccups began.

Roentgen examination was made. The empty stomach yielded yellowish mucus containing bile. There was strong peristalsis of the stomach. The pyloric canal was 21 mm. long. After two and one-half hours, one fourth of the barium meal was retained in the stomach.

On September 17 the patient was operated on by Dr. van der Loo. The hypertrophic muscle was 21 mm. long.

The patient vomited only once after the operation. He was discharged on September 27.

Case 7.—Hendrik S., aged 4 weeks, was admitted to the hospital on Sept. 10, 1931. His weight was 2,800 Gm. During the week prior to admission he had vomited, with increasing violence, after breast feeding, sometimes before but usually immediately or some time after nursing. A cousin of the patient was operated on for congenital pyloric stenosis. We noticed severe tonic spasm of the stomach while the patient was nursing; no peristalsis was noticeable.

On September 11 roentgen examination was made. The barium suspension flowed immediately through the long, wide pyloric canal; afterward the canal closed tightly and nothing passed for two and one-half hours. There was strong peristalsis of the stomach. The duodenum threw only a slight shadow; the pyloric canal measured 17 mm. in length and was outlined with regard to the duodenum by the partly unfolded bulbus duodeni.

On September 12 edema of the extremities was noted. The patient was operated on by Dr. Verbeek. The pyloric muscle, which was 16 mm. long, was cut.

On September 17 the edema had disappeared. The patient vomited a few times a day.

On October 2 the patient still vomited once or twice a day. Roentgen examination showed strong peristalsis of the stomach. The pyloric canal was funnel-shaped.

Case 8.—Pieter T., aged 8 weeks, was admitted to the hospital on Dec. 1, 1931. His weight was 3,200 Gm. He had been bottle fed and had vomited in increasing measure since the eighth day after birth. While feeding, at first only tonic spasm of the stomach was noticed, extending within 3 cm. to the right of the umbilicus. When 200 cc. of nourishment was given, strong peristalsis and typical vomiting followed.

On December 2 roentgen examination was made. The empty stomach contained from 1 to 2 cc. of fluid. The pyloric canal was 16.5 mm. long. A small quantity of barium penetrated into the folds of the canal (fig. 1 *D*). After three and one-half hours about one half to one third of the barium meal was still in the stomach.

On December 3 the patient was operated on by Dr. Verbeek. The pyloric muscle, 15 mm. long, was cut.

The patient vomited only once after the operation. He was discharged on December 29.

The group of cases just described do not give a different point of view than those reported in our previous article on the same subject. The pyloric canal was generally very long and narrow; occasionally it seemed to be wide when the barium suspension penetrated the folds of the mucous membrane. As Voss [2] noted, the canal was sharply outlined in respect to the shadow of the stomach. The unfolding of the duodenum varied, and with regard to it the outline of the canal could sometimes not easily be distinguished. Case 2 shows that it is sometimes impossible to fill the pyloric canal.

In these cases the length of the shadow of the pyloric canal varied from 16.5 to 24 mm. In the former article the variation was from 12 to 23 mm. Usually the measurement can be taken accurately, but it may happen that on account of a curved form the measurement is more or less inexact. When making the films, great care should be taken that the pyloric canal appears on the film in its longest dimension, and therefore the position should be sought in which it runs parallel to the photographic plate. When a fluoroscopic view shows the canal in the proper position, this position should be maintained while taking the film.

The actual length of the muscle can be calculated by taking into account the distance from the focus of the x-ray tube to the pylorus and the distance from the focus of the x-ray tube to the film. In the cases just reported the distance from the focus of the tube to the pylorus was about 63 cm. The distance from the tube to the film was 70 cm. The measurements on the film ought to be multiplied by 63/70, or 0.9, in order to obtain the actual length of the pyloric canal; these lengths ought to correspond to those obtained at the operation (the length of the cut muscle to be measured on the mucous membrane).

In six of the cases the length obtained at the operation differed little from the actual (calculated) length; in one case only was the difference a little more than 2 mm.

A group of seven cases follows in which the canal was shorter and in only two of which operation was performed.

CASE 9.—Toosje v. d. W., aged 5 months, was admitted to the hosiptal on Nov. 10, 1931. Her weight was 4,700 Gm. She had vomited violently since the second week after birth, sometimes before and sometimes after taking a meal. Hiccups frequently occurred, and she did not thrive. While under observation the child did not vomit but often swallowed air. Peristalsis was absent.

On November 25 roentgen examination was made. The stomach emptied quickly. The pyloric canal was decidedly too long (10 mm.). On fluoroscopy it appeared at one time to be narrow and then to be large. No operation was performed.

Data on the Cases Reported

Name	No.	Length of Pyloric Canal, Mm.			Peristalsis or Spasm	Vomiting	Retention Within 3 Hours
		On Film	Calculated	At Operation			
Cases Reported in Former Article							
M. D.	8	23	....	..	Strong	Violent	Much in 2 hours
Fr. Sw.	11	21	....	..	Strong	Violent	Much in 2 hours
H. F.	7	20	....	..	Strong	Violent	Much in 2 hours
A. v. H.	12	19	17.1	18	Strong	Violent	?
A. d. W.	6	19	....	..	Strong	Violent	Much in 2 hours
W. d. J.	9	14	....	..	Strong	Violent	Much
M. G.	13	13	....	..	Strong	Present and then stopped	Much in 2½ hours
W. F.	10	12	....	..	Strong	Violent	Much
Cases Reported in This Article							
N. B.	2	?	....	..	Strong	Violent	Much
C. K.	3	24	21.6	21	Strong	Violent	Two thirds
M. Sch.	4	21	18.9	19	Strong	Violent	Four fifths
F. K.	6	21	18.9	21	Strong	Violent	One fourth
J. V.	5	19	17.1	18	Strong	Violent	Whole
H. S.	7	17	15.3	16	Strong	Violent	Four fifths in 2½ hours
P. T.	8	16.5	14.9	15	Strong	Violent	One half to one third
A. A.	1	11	....	..	Distinct	Absent	One half
T. vd. W.	9	10	....	..	Absent	Absent	?
L. B.	10	7	....	..	Slight	Moderate	None
Th. v. L.	11	7	....	..	Distinct	Moderately strong	One third
W.B.	12	6.5	5.9	5	Slight	Moderate	One half to one third
J. S.	13	6	5.4	4.5	Only indicated	Present	One fifth
W. D.	14	4	....	..	Absent	Present	One sixth to none
R. v. V.	15	4	....	..	Absent	Absent	None
P. G.	16	3	....	..	Absent	Absent	A trace in 2½ hours
N. O.	17	1.5	....	..	Absent	Absent	None

CASE 10.—Leo B., aged 9 weeks, was admitted to the hospital on April 29, 1932. His weight was 3,500 Gm. He had vomited since birth after breast feeding, since the third week in increasing measure. At the time of admission he vomited violently before and after nursing but was growing a little. While nursing there was slight but distinct peristalsis in the region of the stomach; he vomited with moderate force.

Roentgen examination was made. No secretion was obtained from the empty stomach. The pyloric canal was abnormally long (7 mm.). After three hours the stomach was empty. The patient was cured by internal therapy.

CASE 11.—Theo v. L., aged 11 weeks, was admitted to the hospital on March 21, 1932. His weight was 3,000 Gm. The patient vomited during the first ten days after birth, when he was breast fed. Vomiting then stopped, but it started again

about a week prior to admission. The patient then vomited all nourishment (artificial feeding) with moderate force. While nursing he vomited all the nourishment given. Peristalsis in the region of the stomach was not accentuated but was distinct.

On March 25 roentgen examination was made. No secretion was obtained from the empty stomach. The pyloric canal was too long (7 mm.). After three hours one third of the barium meal was still in the stomach.

On April 10 vomiting had been stopped by frequent feeding.

On April 17 the patient received six meals regularly. Normal growth was taking place. He had ceased to vomit.

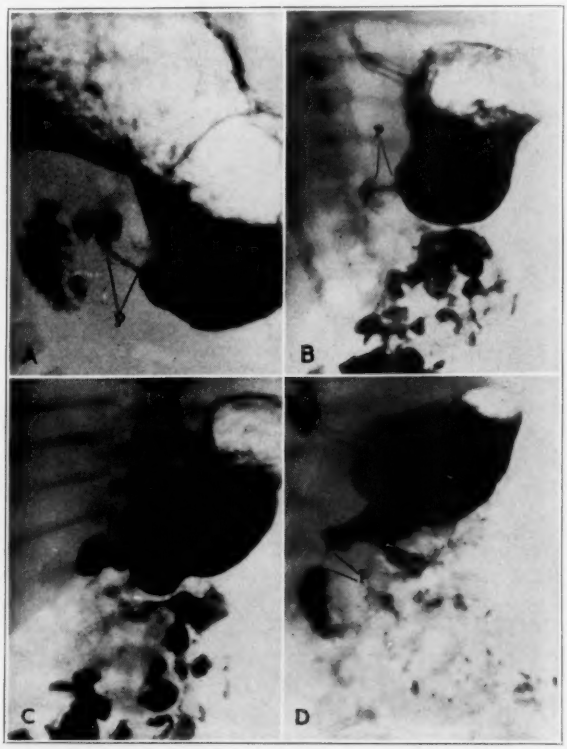

Fig. 2.—*A* shows the pyloric canal in case 1, 11 mm. long; *B* and *C*, that in case 12, 6.5 mm. long, but wider in *C* than in *B*, and *D*, that in case 14, 4 mm. long.

CASE 12.—Willem B., aged 4 days, was admitted to the hospital on Nov. 16, 1931. His weight was 2,700 Gm. The patient since birth had vomited violently all nourishment; the vomitus was yellow. During nursing there was some peristalsis in the region of the stomach and around the umbilicus. After 40 cc. had been ingested violent vomiting occurred, followed by tonic spasm which lasted a long time.

On November 17 roentgen examination was made. The pyloric canal was abnormally long (6.5 mm.). Figure 2 *B* shows it to be very narrow; then again it is very large and filled (fig. 2 *C*). After one and three-fourths hours scarcely

one third of the barium meal had passed into the intestines. After eight and one-half hours there remained some barium in the stomach.

On November 12 the patient was a month old and weighed 3,050 Gm. He vomited with moderate force a few times a day. The vomitus was yellow. There was distinct tonic spasm of the stomach; peristalsis was never very pronounced, there being at most a few waves.

On December 14 roentgen examination gave the same results as on the previous occasion. After three and one-half hours half of the barium meal was retained in the stomach.

On December 15 the patient was operated on by Dr. Verbeek. The pyloric muscle, which was 0.5 cm. long, was cut.

On Jan. 21, 1932, the patient was 10 weeks old and weighed 3,600 Gm. He vomited a few times a day but was discharged.

CASE 13.—Johan S., aged 2½ months, was admitted to the hospital on Oct. 15, 1931. His weight was 2,900 Gm. He had vomited a great deal after every meal since birth, but not violently. The mother suffered from goiter and was nervous. Her other babies had not vomited. During the time of the observation there was never decided peristalsis.

On Oct. 19, 1931, roentgen examination was made. There was no secretion from the empty stomach. The pyloric canal was too long (6 mm.), and now wide, then narrow. After three hours the stomach retained one fifth of the barium meal.

On November 2 the patient vomited continually but not violently. There was some indication of peristalsis; only once a distinct wave was seen.

A second roentgen examination was less convincing than the first. There was little retention of barium in the stomach.

The patient was operated on by Dr. Verbeek. The pathologic pylorus muscle, which was 4 by 5 mm. long, was cut.

On November 12 the patient vomited small quantities frequently. He was discharged.

CASE 14.—Waltera D., aged 5 weeks, was admitted to the hospital on March 4, 1932. Her weight was 3,000 Gm. The patient had vomited violently since birth at different times after feeding. Her brothers and sisters had suffered from the same trouble during infancy. After taking a meal of 100 cc., the stomach outline was distinctly visible, and the patient vomited small quantities. Peristalsis was not distinct.

On March 9 roentgen examination was made. The pyloric canal was undoubtedly too long (4 mm., fig. 2 *D*), and on some films it seemed very narrow. On the fluoroscopic screen it unfolded properly. After three hours there was distinct retention in the stomach, about one sixth of the barium meal given.

On March 30 the patient vomited small quantities violently a few times a day. A second roentgen examination was made. The barium suspension passed quickly. The pyloric canal was long but entirely unfolded. There was no retention after three hours.

On June 8 the patient was 4 months old and weighed 4,250 Gm. He vomited copiously after each feeding.

On roentgen examination, the barium passed quickly. The length of the pyloric canal is the same, but the canal unfolded properly. After three hours there was only a coating of barium on the wall of the stomach.

CASE 15.—Rudolphina v. V., aged 2½ months, was admitted to the hospital on Oct. 7, 1931. Her weight was 2,840 Gm. She did not thrive and vomited little if at all. There was no peristalsis of the stomach.

On October 9 the patient vomited; there was a trace of blood in the vomitus.

On November 27 roentgen examination was made. There was no secretion from the empty stomach. The barium passed quickly. The pyloric canal filled properly but was decidedly lengthened (4 mm., fig. 3 *A*). After three hours the stomach was empty.

On December 25 the patient weighed 4,700 Gm. She seemed mentally abnormal. She was discharged.

In the group of cases just described, the length of the pyloric canal was from 4 to 11 mm. according to the measurements taken on the

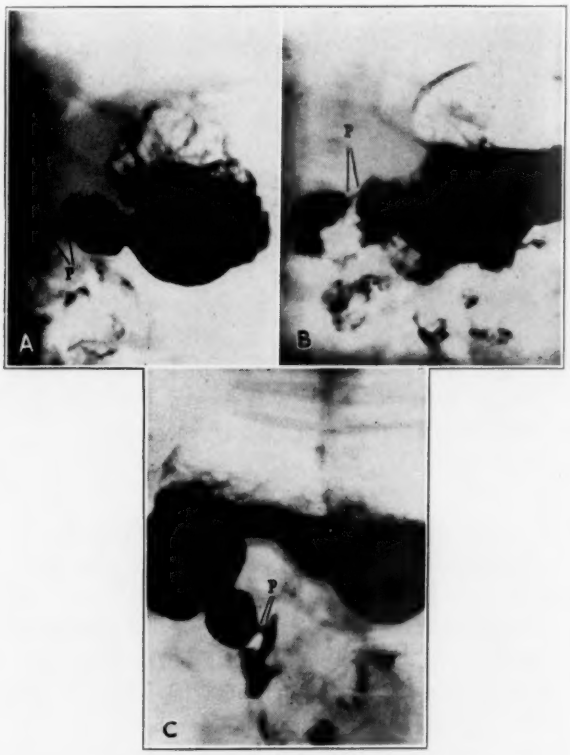

Fig. 3.—*A* shows the pyloric canal in case 15, 4 mm. long; *B*, that in case 16, 3 mm. long, and *C*, that in case 17, 1.5 mm. long.

film. In two cases it was possible to determine the actual length during the operation; this did not differ much from the length calculated.

The pyloric canal is sometimes narrow and again wide and filled. These changes are caused by the retraction and expansion of the muscle at a given moment. This causes the shadow of the pyloric canal to be often indistinct in outline with regard to the shadow outline of the stomach.

Two further observations follow:

CASE 16.—P. G., aged 3 months, was admitted to the hospital on May 15, 1931. He did not vomit. Roentgen examination showed the pyloric canal to be 3 mm. long (fig. 3 *B*). After two and one-half hours a small amount of barium was left in the stomach.

CASE 17.—Nelly O., aged 3 months, was admitted to the hospital on May 11, 1931. She did not vomit. Roentgen examination showed the pyloric canal to be 1.5 mm. long (fig. 3 *C*). After two and one-half hours the stomach was empty.

COMMENT

In our opinion it is possible to secure good roentgenograms of the pyloric canal in infants and even to determine with sufficient accuracy its length. This is accomplished by multiplying the length on the film by a factor which allows for the enlargement on the film. This factor is found in the equation: distance from focus of tube to pylorus ÷ distance from focus of tube to film. With our apparatus this is 63/70, or 0.9.

There were nine cases in which the two measurements could be exactly made. Only slight differences were noted between the measurements calculated and those taken during operation. The greatest difference observed was 2.1 mm. and, the difference in another case was 1 mm. In all other cases the difference was less than 1 mm. (table). We are justified, therefore, in concluding that there is a definite connection between the length of the pyloric canal on the film and its actual length.

In the cases reported in our former paper and those described here, the lengths of the pyloric canal observed (on the film) were as follows: 24, 23, 21, 20, 19, 17, 16.5, 14, 13, 12, 11, 10, 7, 6.5, 6, 4, 3 and 1.5 mm.

The fact that there is such a difference in the length of the pyloric canal makes it probable that we have to do with an anomaly and that the conditions that may lead to the clinical picture of congenital hypertrophic pyloric stenosis are produced when the pyloric canal (pyloric muscle) exceeds a certain length. This supposition is supported by the table, in which are also mentioned the cases reported in our former article. The cases are listed according to the length of the pyloric canal. In the columns we state the presence or absence and the degree of the concomitant symptoms: peristalsis or tonic spasm, vomiting and retention of the barium meal within three hours. It is obvious that these symptoms are distinctly present only when the length of the pyloric canal (length of the muscle) exceeds 6 mm.

CONCLUSIONS

1. The actual length of the pyloric canal, from which the length of the pyloric muscle differs only slightly, is found by measuring the

length on the film and taking into account the factor of the magnification caused by projection on the film.

2. The length of the pyloric canal varied in our study from 1.5 to 24 mm. (measurements on the film).

3. When the length of the pyloric canal exceeds 6 or 7 mm. the conditions are present that may cause the clinical picture of congenital hypertrophic pyloric stenosis.

CORRECTION

In the article by Dr. Chi Che Wang in the November issue (Am. J. Dis. Child. **48**:1041, 1934), there are three errors in the third column from the right of table 1, on page 1043, i. e.:

+ 2.7 should read −4.5
+ 4.3 should read −6.9
+ 14.0 should read + 1.8

Case Reports

SPORADIC CRETINISM IN ONE OF TWINS

REPORT OF CASES WITH ROENTGEN DEMONSTRATION OF OSSEOUS CHANGES THAT OCCURRED IN UTERO

GEORGE B. DORFF, M.D.

BROOKLYN

The more important features to be presented here are:

1. There is definite proof that the retarded osseous development in congenital sporadic cretinism has its origin in utero.

2. There is an apparent relationship of this osseous retardation to a disturbance of the thyroid gland in the fetus.

3. Two additional cases of cretinism in one of differently sexed fraternal twins are reported, with roentgen demonstration of the occurrence of osseous retardation in utero in one case.

4. The probable deductions that may be made in the physiology are discussed.

A review of the American literature shows the paucity of reports on sporadic cretinism in twins. Two cases were reported by Gordon [1] in a review of a series of three hundred and forty cases of myxedema in childhood in North America. In his series he cited one case reported by Charles Herrman,[2] in male twins, 6½ years of age, one twin being normal. Another, though rather atypical, case was reported by Manson,[3] a case of myxedema in both brothers, aged 11½ years. Petschacher [4] also briefly reported the occurrence of myxedematous cretinism in 14 year old twins.

As far as I know, retarded osseous development occurring in utero, however, has never been demonstrated in congenital sporadic cretinism, although both Engelbach [5] and Shelton [6] mentioned it as an aid for the early recognition of congenital cretinism.

Presented before the New York Endocrinological Society, Dec. 29, 1932.

From the endocrine clinics of the Department of Pediatrics of New York University and Medical College and of Bellevue Hospital, Dr. Charles Hendee Smith, Director of Pediatrics.

1. Gordon, M. B.: Childhood Myxedema or So-Called Sporadic Cretinism in North America, Endocrinology **6**:234 (March) 1922.

2. Herrman, C.: Sporadic Cretinism: Clinical Study of Forty-One Cases, New York State J. Med. **14**:394, 1914.

3. Manson, L. S.: Unusual Manifestations in Cretinism, M. Rec. **77**:7 (Jan. 1) 1910.

4. Petschacher, W.: Wien. klin. Wchnschr. **35**:749, 1922.

5. Engelbach, W.: Endocrine Medicine, Springfield, Ill., Charles C. Thomas, Publisher, 1932, vol. 2, p. 91.

6. Shelton, E. K.: Roentgenographic Studies in Normal Osseous Development, J. A. M. A. **96**:759 (March 7) 1931.

REPORT OF CASES

I therefore present the following reports on two patients treated for glandular disorders at children's endocrine clinics at Bellevue Hospital and Medical College:

CASE 1.—S. W., a boy, aged 17 months, with congenital hypothyroidism and myxedema, had a fraternal twin girl, B. W., who was normal. A normal female sibling, D. W., had been born subsequently.

S. W. was admitted to the endocrine clinic on Nov. 12, 1931, with the complaint by the mother that the child did not sit up, had no teeth and was not developing as rapidly as the twin sister. The patient was born in New York on June 4, 1930,

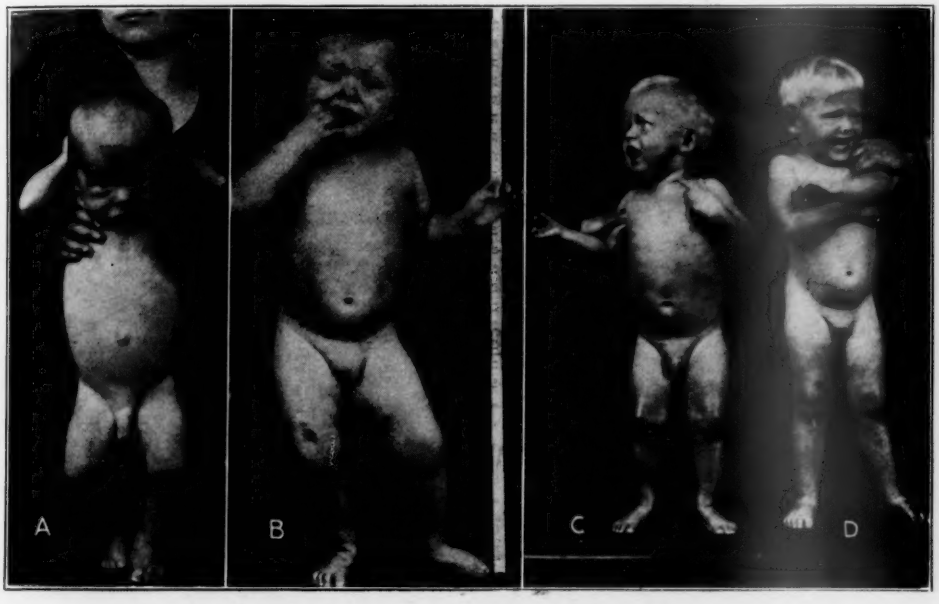

Fig. 1 (case 1).—Photographs showing: *A*, S. W., aged 17 months, a cretin, before treatment; *B*, B. W., aged 17 months, the normal twin sister; *C*, S. W., aged 28 months, after ten months of thyroid therapy, and *D*, B. W., aged 28 months, the normal twin sister.

normally at full term with a birth weight of 5¾ pounds (2,608 Gm.). The other twin was normal in every respect, and the father and mother were apparently normal. The mother had no complications prepartum or post partum. There were no previous pregnancies. The patient had slight jaundice for three months, probably not true jaundice, but the sallow complexion characteristic of the cretin. Otherwise he was apparently well in early infancy.

Physical examination showed a white male child with the typical signs and symptoms of cretinism. The twin sister, on examination, was found to be normal in every respect. The Wassermann reaction of the blood was negative for both. A roentgenogram of S. W., taken previously in the general clinic (Nov. 2, 1932) at the age of 17 months for a routine examination for rickets, showed marked

retardation of the osseous system (fig. 2), which is characteristic of thyroid insufficiency. There was no roentgen or clinical evidence of rickets. Thyroid extract was prescribed and the patient made rapid progress in his development, as evidenced both clinically and roentgenologically (table and fig. 2).

The mother again became pregnant after the birth of the twins and on Dec. 6, 1932, gave birth to a normal female child (D. W.), who weighed 9 pounds (8,082 Gm.). A roentgenologic study of the bones and several clinical examinations have indicated that the child at this writing is apparently normal.

Roentgen plates taken of B. W. (twin sister) at the age of 19½ months disclosed the presence of two centers of ossification in the carpus, the presence of the

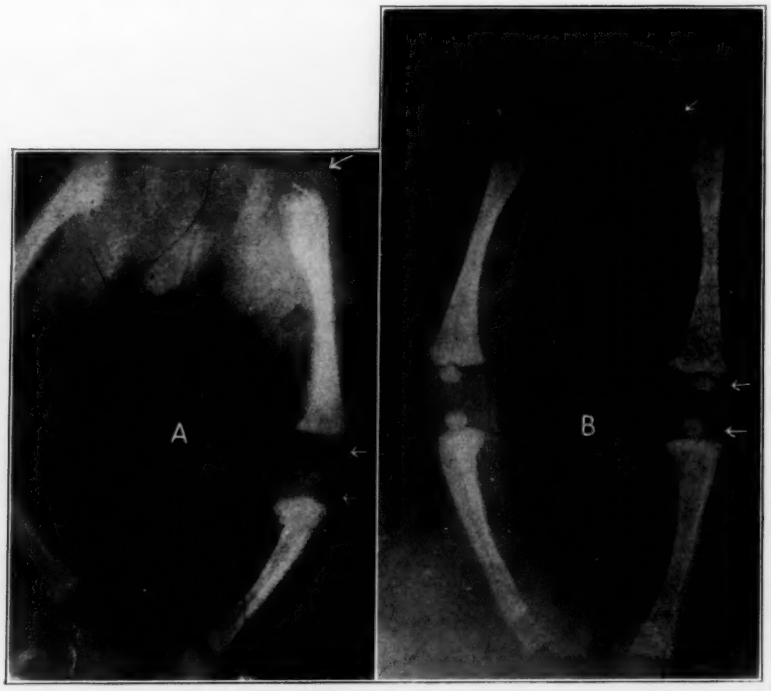

Fig. 2 (case 1).—*A,* roentgenogram of S. W., a cretin, aged 17 months. This is a poor plate, taken as part of the routine examination in the general clinic for evidence of rickets. It is clear enough to show the absence of femoral and tibial epiphyses and underdeveloped pelvic bones. *B,* S. W., aged 20½ months, after three and a half months of thyroid therapy. The advancement in the development of bone is notable.

distal epiphysis of the radius and several of the epiphyses for the proximal row of phalanges. The superior epiphysis of the tibia and the inferior epiphysis of the femur, the inferior epiphyses of the tibia and the fibula and four tarsal centers of ossification were present and well formed. The ilium, ischium and pubic ossifications were well developed, and the epiphysis for the head of the femur was well formed. The capitellum of the humerus was present. This is a normal osseous picture. The sella turcica was apparently normal in each twin.

Case 2.—M. K., a girl, aged 9½ years, had congenital hypothyroidism with myxedema; the fraternal twin, a boy, N. K., was normal.

The patient had been treated in the general clinic since early infancy. The complaint, as in case 1, was the failure to develop as rapidly as the normal twin. The patient was born in New York, at full term of normal parents. There was

Record of Development of Patient in Case 1 Under Treatment

	11/2/31 Age, 17 Mos.	Normal Time of Appearance	1/19/32 Age, 19½ Mos. (2½ Mos. of Thyroid Therapy)*	2/20/32 Age, 20½ Mos. (3½ Mos. of Thyroid Therapy)	7/14/32 Age, 25 Mos. (8 Mos. of Thyroid Therapy)
Inferior femoral epiphysis	Absent	Present at birth in 100% unless there is frank prematurity;† present at birth in 100% [6]	.....	Present	.....
Superior epiphysis of tibia	Absent	Normally present at birth in 75-80% of cases;† present at birth [6]	.....	Present	.....
Inferior epiphysis of tibia	Absent	Appears at 1 year [6]	.....	Absent	.....
Inferior epiphysis of fibula	Absent	Appears at 2 years [6]	.....	Absent	.....
Pelvic ossification	Small ossifications of ilium, ischium and pubis	Appears at the fourth or fifth fetal month,‡ and should be fairly well formed at birth	.....	Better formed	.....
Tarsal centers	Three small tarsal centers present	Talus and calcaneus usually present and well formed at birth, cuboid in 60% at birth;† all three present at birth [6]	.....	Three or four tarsal centers of fair size present	.....
Epiphysis for head of femur	Absent	Appears at 1 year [6]	.....	Absent	.....
Carpal centers	Absent	Os capitatum and os hamatum appear at about six months [6]	Absent	.....	Two centers present
Phalangeal and metacarpal epiphyses	Absent	Appear at from 2 to 2½ years [6]	Absent	.....	Absent
Distal epiphysis of radius	Absent	Appears at from 6 to 8 months [6]	Absent	.....	Small epiphysis present
Capitellum of humerus	Absent	Appears at 2 years [6]	.....	Absent	.....
Epiphysis for head of humerus	Absent	Appears at birth, or within the first few months;§ during the first year [6]	.....	Very small	.....

* Thyroid therapy was instituted on Nov. 12, 1932.

† Adair, F. L., and Scammon, R. E.: A Study of the Ossification Centers of the Wrist, Knee and Ankle at Birth, with Particular Reference to the Physical Development and Maturity of the Newborn, Am. J. Obst. & Gynec. **22**: 35, 1921.

‡ Cunningham, D. J.: Textbook of Anatomy, ed. 5, New York, William Wood & Company, 1921, p. 235.

§ Paterson, R. S.: Some Factors Influencing Epiphyseal Growth and Union, Am. J. Phys. Therap. **6**: 64 (May) 1929.

no evidence of endocrine disturbance in the mother during her pregnancy. The weight of the patient at birth was 9½ pounds (4,309 Gm.) while that of the normal brother was 7½ pounds (3,307 Gm.). Two weeks after birth the patient "caught cold and has never been well since." The first examination at the age of 1 year showed all the evidences of cretinism with myxedema, and the patient was given small doses of thyroid extract, which, however, were taken very irregularly. I first saw the child when, at the age of 9½ years, the diagnosis of sporadic

cretinism was confirmed. A roentgen examination of the ossifications of the wrists and hands showed a development of bone equivalent to the normal for about 6 years. The roentgenologic and physical examination of the brother, N. K., revealed no abnormalities. Increased doses of thyroid extract were then prescribed and taken regularly, with subsequent marked improvement.

COMMENT

S. W. (case 1), at the age of 17 months showed definite retardation of osseous development, as revealed by the absence of the inferior epiphysis of the femur, of the inferior epiphysis of the tibia, of the carpal centers of the distal epiphysis of the radius, of the epiphysis for the head of the humerus, of the epiphysis for the head of the femur and delayed development of the primary ossifications of the pelvis. Since normally many of these ossifications either develop within the first year or are present at birth, one must deduce that this osseous retardation occurred during the fetal period and was truly congenital. That sporadic cretinism is congenital is today admitted.[7]

As to the cause for the deficient thyroid gland in S. W. in utero, Thomas [8] expressed the belief that it might have resulted from a slowly progressing inflammatory process in utero. Thyroiditis with consequent thyroid atrophy is frequently mentioned as following acute infectious diseases,[9] and even infections in the mother during pregnancy may be transmitted through the placenta to the fetus, setting up a similar infection there with involvement of the thyroid gland.[10]

Why the thyroid gland above all other tissues should be the *locus minoris resistentiae* is not clear. It is hard to understand, too, why, under similar environmental conditions in utero the thyroid gland of one of each set of twins was apparently completely destroyed, and that of the other twin showed no apparent effects. If, on the other hand, the inflammatory process of the thyroid gland was an early postnatal occurrence, how can the retarded osseous development which must have occurred in utero be explained?

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7. (*a*) McCarrison, Robert: The Thyroid Gland in Health and Disease, New York, William Wood & Company, 1917. (*b*) Crotti, A.: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1918, p. 89. (*c*) Engelbach.[5]

8. Thomas, Erwin: Personal communication to the author.

9. (*a*) Siegert, F.: Affections of the Thyroid, in von Pfaundler, M., and Schlossmann, A.: Diseases of Children, translated by S. W. Kelly, Philadelphia, J. B. Lippincott Company, 1912, vol. 3, p. 534. (*b*) Zondek, H.: Thyroid Destruction After Infections, in Die Krankheiten der Endokrinen Druesen, ed. 2, Berlin, Julius Springer, 1926. (*c*) Crotti,[7b] p. 191.

10. (*a*) DeLee, J. B.: The Principles and Practice of Obstetrics, ed. 4, Philadelphia, W. B. Saunders Company, 1924, pp. 61, 351 and 509. (*b*) Spalding, H.: Variola, in Abt, I.: Pediatrics, Philadelphia, W. B. Saunders Company, 1925, vol. 6, pp. 152 and 163.

That infectious thyroiditis with resultant thyroid atrophy and hypothyroidism is a rarity has been shown by Hagenbuch,[11] Joll,[12] Gordon [1] and Osler.[13]

The facts presented thus far point to the unlikelihood of an inflammatory process causing the deficiency of the thyroid gland. I favor the view that this was caused by a disturbance in the germ plasm for the anlage of the thyroid gland.

Various questions arise: 1. Is there a need for a thyroid hormone in the embryo and fetus? 2. Is there fetal thyroid activity? 3. Does the mother normally supply a thyroid hormone to the offspring in early pregnancy and in later fetal life? 4. Is there a storing of the thyroid hormone in the fetus at the end of pregnancy to tide the new-born over the first few months? 5. Is there placental permeability to the thyroid hormone?

There is not at present sufficient direct evidence for a definite answer to these questions. However, the following views are briefly presented:

Needham [14] in speaking of the lower forms of mammals said, "It is probable that no hormones exist in the undeveloped egg, but they rise in a definite succession during development." [15] The egg develops, its cells multiply, and it grows larger and later begins to differentiate. Bearing no prepared hormone, the growth of this egg must be carried on by the autochthonous impulses of the cells of the organism. The embryo grows, and grows rapidly, even before there is any semblance of the thyroid gland or of any well differentiated organs that may possibly function. After a sufficient amount of growth has taken place a primary or nonfunctional (Needham) differentiation of the rudiments of the different organs are determined. This process is probably also influenced by the autochthonous stimulus of the cells and not by any glandular secretions. There then occurs the stage of secondary or functional differentiation in which the inception of active function by the new organs, with important consequences, occurs. At this point the presence of an active thyroid gland may be conceded, which may in a great part deter-

11. Hagenbuch, M.: Beitrag zur Kenntnis der Strumitis, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:181; 1921.

12. Joll, C. A.: Diseases of the Thyroid Gland, London, William Heinemann, 1932, p. 78.

13. Osler, W., and McCrae, T.: The Principles and Practice of Medicine, ed. 9, New York, D. Appleton & Company, 1922, p. 863.

14. Needham, J.: Chemical Embryology, London, Cambridge University Press, 1931, vol. 1, p. 444; vol. 3, p. 1506.

15. Needham,[14] footnote, p. 1358: "This must obviously be qualified by reference to the findings of an insulin-like substance in bird and fish egg-yolks (Shikinami, Y.: Ueber die Hypoglykämie erzeugenden Stoffe aus verschiedenen tierischen Substanzen, besonders aus Eigelb des Hühnereies, Tohoku J. Exper. Med. **10**:1, 1928) and a thyroxin-like substance in echinoderm eggs (Carter, G. S.: Iodine Compounds and Fertilization, J. Exper. Biol. **8**:176, 1931)."

mine the subsequent development of the fetus for the remaining period of its existence in utero and thereafter. At this stage any defect in the development of the thyroid anlage will make itself evident through disturbances of the metabolic processes of the fetus. Yet even here the fetus still has the power of growth; but its growth is not the same as in the fetus with a functionally normal thyroid gland. The athyreotic fetus with complete absence of the thyroid gland does not stop short in its growth, even in utero; it continues to grow, but at a slow and protracted pace; its functional differentiation, however, is much retarded.

In the latter part of fetal existence there is probably some activity of the fetal thyroid gland, but not to a great extent. Elkes [16] was unable to demonstrate the presence of colloid formation in the thyroid gland of the fetus at 4½ months. Lucas Keene and Hewer [17] found traces of colloid in the fetal thyroid at 11 weeks and concluded from the histologic appearance that at full term the thyroid gland of the human fetus is actively secreting. Fenger [18] showed the presence of iodine in the human fetus in the latter months. Thomas and Delhougne [19] also showed the presence of iodine in new-born and in certain premature infants. Thomas [20] expressed the belief that the thyroid gland is complete in its development at the end of fetal life, and that as early as the fourth fetal month the organ looks entirely as in later life. Crotti,[21] too, was of the opinion that there is fetal thyroid activity, and he could not agree with Langhans, Kaufmann and Bircher that the fetal thyroid gland is normally physiologically inactive. He said:

> Although it is highly probable that the functions during fetal life are diminished, it is, nevertheless, difficult to admit that the gland is in a state of complete physiological negativism. Let us not forget that there is a period, the vesicular stage, during fetal life when well-formed alveoli containing colloid are present. Nothing proves that the thyroid at that time does not functionate.

Although the fetus in utero has all the vital functions, the aid of the placenta and the environment of the fetus are such that it does

16. Elkes, C.: Der Bau der Schilddrüse um die Zeit der Geburt, Dissert., Koenigsberg, 1903.

17. Keene, M. F. L., and Hewer, E. S.: Glandular Activity in the Human Fetus, Lancet **2**:111, 1924.

18. Fenger, F.: On the Iodine and Phosphoric Contents, Size and Physiological Activity of the Fetal Thyroid Gland, J. Biol. Chem. **14**:397, 1913; On the Presence of Iodine in the Human Fetal Thyroid, ibid. **20**:695, 1915.

19. Thomas, E., and Delhougne, E.: Studien an Schilddrüsen von Kölner Kindern bezüglich des Jod- und Kolloidgehaltes, Virchows Arch. f. path. Anat. **248**:201, 1924.

20. Thomas, E.: Drüsen mit innerer Sekretion, in von Brüning, H., and Schwalbe, E.: Handbuch der allgemeinen Pathologie und der pathologischen Anatomie des Kindesalters, Munich, J. F. Bergmann, 1913, vol. 2, p. 322.

21. Crotti,[7b] p. 191.

not require a high metabolic rate to carry on those functions.[22] The normal fetus with a normal thyroid gland meets the needs without difficulty; the fetus with absence of this gland or a deficient gland will show evidences of impaired function (retarded development). However, after leaving the environment of the uterus the infant is called on to meet greater demands, and the one with a disturbed thyroid gland will soon show signs of the lack of thyroid hormone.[23] The time of onset of the symptoms depends on the amount of thyroid remnant still functioning and the metabolic demands made on the infant in performing its own functions.

Siegert [9a] said that in cretins with a complete absence of the thyroid gland such signs as macroglossus, pallor and obstipation may be apparent at birth or shortly thereafter. In addition to the symptoms that Siegert listed I wish to emphasize and demonstrate that there will also be evident, roentgenologically, a retardation of osseous development in the new-born.

When a delay of signs and symptoms in the infant with absence of the thyroid gland occurs, some say that the normal mother either supplied the fetus in its later intra-uterine period with a sufficient store of thyroid hormone to tide it over its early postnatal period, or that the thyroid hormone is being supplied to the infant through the mother's breast milk. Thomas said that the function of the mother is to provide for the offspring an effective thyroid secretion. This task she can accomplish only if she is functioning completely. Kocher,[24] in 1892, first recognized that the mother's thyroid gland can act vicariously for that of the fetus. Siegert,[25] in 1921, also expressed the opinion that the mother can act both for herself and for the fetus, if the latter's thyroid gland does not function. However, it is apparent from the histories that the mothers of the patients reported here, particularly the mother in case 1, did not perform this function.

The fact that the maternal incretory glands hypertrophy during pregnancy does not necessarily prove that the glands of the fetus are inactive, and that the mother is supplying the extra hormone to the fetus. Certainly, if there were a vicarious maternal supply of thyroid hormone to the fetus by a mother functioning normally the osseous development of S. W. (case 1) should at least have been normal for the length of the intra-uterine period, since the mother was apparently functioning

22. Grulee, C. G.: The Newborn: Physiology and Care, New York, D. Appleton & Company, 1926, vol. 2, p. 97. DeLee.[10a]

23. Falta, W.: Endocrine Diseases, translated by M. K. Myers, Philadelphia, P. Blakiston's Son & Company, 1923, p. 41.

24. Kocher, T.: Zur Verhütung des Cretinismus und cretinoider Zustände nach neueren Forschungen, Deutsche Ztschr. f. Chir. **34**:556, 1892.

25. Siegert, F.: Zur Frage des angeborenen und erworbenen infantilen Myxoedems, Verhandl. d. Gessellsch. f. Kinderh., 1921, p. 364.

normally. Even if there was any cause in its early postnatal period to injure the new-born infant's thyroid gland, i. e., by a postnatal inflammatory process, S. W. should have presented at 17 months an osseous development equivalent to that of a normal new-born child. This was not the case. Were one to admit that the inferior epiphysis of the femur may occasionally be absent in the normal new-born child,[26] and were one to admit that the three tarsal ossifications, as seen in the roentgenogram, are normal for the newly born, it would nevertheless have to be granted that a comparison of the first roentgenogram of S. W. at 17 months with that of a normal new-born child would show a definite retardation in the development of the entire skeletal system.

The statement that maternal thyroid hormone is carried in the breast milk and provides the newly born with sufficient secretion for a time is questioned, for Gordon [1] and Herrman [2] found that breast feeding had apparently no influence on sporadic cretinism in the infant since the condition developed in a number of children while at the breast.

Whether a hormone can be transmitted from the mother to the fetus or from the fetus to the mother via the placenta has not as yet been definitely shown. I am in accord with Needham [14] in his belief that no coherent theory of absolute placental permeability can be found. Although the placenta may be permeable to iodine, it does not necessarily follow that it is permeable to the iodine-containing thyroxine.

On the other hand, Thomas [27] expressed the belief that "under pathological conditions the fetus may act vicariously for the mother." Whether in certain reported cases the alleviation in the pregnant mother of symptoms of hypothyroidism, diabetes mellitus and Addison's disease was due to a transmission of the hormone from the fetus to the mother via the placenta seems questionable, since the usual hypertrophy of the internal secretory glands of the mother during pregnancy may account for this alleviation.

In conclusion, I am inclined to believe that: 1. In the embryonic and early fetal periods there is no apparent need for a thyroid hormone or for thyroid activity. 2. Later in fetal life, after nonfunctional differentiation has occurred, there follows some activity of the thyroid gland which aids in the functional differentiation of the fetus. 3. In view of the low metabolic requirement of the fetus in utero there is little need for an excessive function of the thyroid gland, and the fetus, as a rule, can meet the demand. 4. When the fetus shows absence of the thyroid gland or a deficient gland the condition is due to a developmental defect of the embryonic cells rather than to an inflammation or

26. Adair and Scammon: A Study of the Ossification Centers of the Wrist, Knee and Ankle at Birth, Am. J. Obst. & Gynec. **22**:35, 1921.

27. Thomas, E.: Innere Sekretion in der ersten Lebenzeit; vor und nach der Geburt, Jena, Gustav Fischer, 1926, pp. 1 and 131.

other exogenous cause. 5. When the fetus has a deficient thyroid gland, there is disturbance in differentiation, as evidenced in part by a retardation of development of the bones. 6. When there is an insufficient thyroid secretion in the fetus, it is not replaced by the mother's secretion at any time, nor is it supplied to the infant later, in any way, by breast milk. 7. Normally, the placenta is probably not permeable in either direction to the thyroid hormone. 8. Though evidence of thyroid insufficiency, such as retarded osseous development, may have been present in the fetus, clinical signs and symptoms may not be apparent in the new-born until there is a need or a demand for greater metabolic function. 9. The time of appearance of symptoms of thyroid insufficiency necessarily depends on the amount of functional thyroid tissue still remaining in the new-born.

SUMMARY

1. A review of the literature reveals a case of sporadic cretinism in one of male twins (the other being normal) reported by Herrman, an atypical case in each of male twins reported by Manson and a third case of suspected cretinism in each of twins reported by Petschacher.

2. Two additional cases are presented in which sporadic cretinism occurred in two sets of differently sexed twins, one twin in each set being involved, the other twin being normal in all respects.

3. For the first time definite roentgen evidence is given that the retarded osseous development in a twin with congenital sporadic cretinism occurred in utero.

4. It is believed that (*a*) there is an independent, low grade fetal thyroid activity which is not directly influenced by the maternal thyroid hormone; (*b*) there is probably no transmission of the thyroid hormone through the placenta from either the mother or the fetus.

5. Stress is placed on the importance of studying the development of the bones in the new-born suspected of hypothyroidism by roentgenograms.

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ACRODYNIA

REPORT OF A CASE WITH A PATHOLOGIC STUDY

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Pathologic studies on acrodynia have been few. Those reported have served more and more to focus attention on the nervous system as the site of the most noteworthy pathologic changes, although a uniform and characteristic pathologic picture is still lacking. The present report gives further evidence of the neurologic nature of this syndrome.

CASE REPORT

History.—L. M., a white girl, aged 4 years, whose family history and past history were negative, during July, 1931, had an unexplained "measles-like" rash without fever which lasted a few days. One month later she became irritable and restless, did not sleep at night and had a very poor appetite. There was itching of the nose and anal region and pronounced pain in various joints and in the lower part of the back. A general maculopapular rash again appeared and the child began to perspire profusely. The mother stated that the hands had a parboiled appearance. The skin of the hands and feet began to peel and there was considerable itching of the extremities.

The patient was admitted to the Children's Hospital on Sept. 29, 1931, with the aforementioned complaints. While there her temperature ranged between 99.6 and 101.8 F., her heart rate varied between 120 and 160 beats per minute and her blood pressure was 140 mm. systolic and 98 mm. diastolic. There was a papular rash about her mouth, extremities, lower part of the abdomen and vulva. She rubbed her hands and feet constantly and the skin of the palms and soles was desquamating in large flakes. The liver was palpably enlarged and the patellar reflexes sluggish. Otherwise the results of the physical examination were not remarkable. The following laboratory data were obtained at this time: red blood cells, 4,496,000; hemoglobin, 84 per cent (Sahli); white blood cells, 10,500; polymorphonuclears, 70 per cent. There were 20 cells per cubic millimeter of spinal fluid, 60 per cent of which were polymorphonuclears. The test for globulin was negative, the sugar content normal and the colloidal gold curve 0011000000. The tuberculin and Wassermann tests and the examination of the stools and urine gave negative results. A diagnosis of acrodynia was made. Two transfusions were given; the patient improved slightly, especially with regard to irritability, and she was allowed to return home on Oct. 18, 1931.

Her symptoms rapidly became worse and on October 23 she was referred to the University of California Hospital with the same complaints: itching, profuse perspiration, sleeplessness and irritability.

From the Departments of Pediatrics and Pathology, University of California Medical School, San Francisco.

Physical Examination.—There was a fine, pinkish, maculopapular rash over the back, chest and abdomen with excoriated areas and crusts from scratching. The skin of the hands (fig. 1) and feet was desquamating and the hands, especially the palmar surfaces, were reddened. The tonsils and pharyngeal tonsils were moderately enlarged. Profuse secretion in the upper respiratory passages caused a nasal discharge, cough and rhonchi. The heart was normal except for a rapid rate of 158 beats per minute. The blood pressure was 138 mm. systolic and 95 mm. diastolic. The edge of the liver was 7 cm. below the costal margin, and the spleen was not palpable. Patellar and abdominal reflexes were absent, the ankle jerks were sluggish, and the biceps and triceps reflexes were normal.

Laboratory Data.—The spinal fluid, taken on October 28, contained 1 cell per cubic millimeter; the Pandy and Wassermann tests were negative; the colloidal gold curve was 0000000000 and the blood culture was also negative. Blood chemistry determinations per hundred cubic centimeters showed the following results:

Fig. 1.—Peeling of the hands in the early stages. Later deep ulcerations of the palmar surface of the fingers developed and amputation of the distal portion of the right index finger was necessary.

serum calcium, 13.8 mg.; plasma chloride, 514 to 560 mg.; serum albumin, 6.7 mg., and serum globulin, 1.6 mg.

The patient (fig. 2) was one of the most unhappy and pitiful children ever seen in the ward. The itching was uncontrollable during most of her eight months' stay and despite the tying down of all the extremities, she managed to cause bleeding in many areas by rubbing. Perspiration drenched her clothes and was not relieved by atropine. She disturbed the ward most of the night, and sleep could not be induced by bromides, phenobarbital, chloral or paraldehyde. She slept fitfully during the day. Her resistance to infection was poor and she suffered from cystitis, a hemolytic streptococcic cellulitis of the vulva and back, an osteomyelitis of the distal phalanx of the right finger which necessitated amputation, and many subcutaneous abscesses in various parts of the body. Her muscles were weak and flabby, particularly those of the shoulder girdle. Her gait was waddling and she was easily fatigued by slight activity. The patellar reflexes were absent on entrance. They were obtained on December 7, at which time the right one was

hyperactive. At all subsequent examinations they were absent, as were the triceps, biceps, abdominal and achilles reflexes. During April a bilateral Babinski reflex was obtained, which later disappeared. A tremor of the eyelids appeared and later bilateral ptosis. The patient had a cretinoid facies with the typical *"unkindlich"* expression. She stammered; her hair began to fall out; the rectum prolapsed. Her pulse remained rapid; the rate varied between 120 and 180 beats per minute and was unaffected by pressure on both vagi or by the administration of atropine. The blood pressure ranged from 108 to 150 mm. systolic and from 68 to 98 mm. diastolic, averaging 128 mm. systolic and 85 mm.

Fig. 2.—Appearance of the patient in November 1931. The diffuse rash, swollen fingers and excoriated abdomen are shown.

diastolic. Her hands were swollen and looked parboiled, with the skin constantly peeling. The patient was rarely afebrile. There was generally a profuse nasal and bronchial secretion which interfered with breathing and clear speech.

For the most part, therapy did not alleviate her symptoms. Atropine was given for sweating, sedatives for itching and insomnia, and various applications for itching. Tonsillectomy, transfusion, ultraviolet rays and a diet containing large amounts of liver and rich in vitamin B, as well as in vitamins A, C and D, failed to bring about any marked improvement.

On the night of June 3, 1932, the patient complained of abdominal pain and vomited. A few hours later she was in a state of shock and a mass was felt in the lower part of the abdomen. Vomiting continued and a diagnosis of intussusception was made. Death occurred quickly while the patient was being prepared for operation.

Observations at Autopsy.—The autopsy was performed three hours and twenty-five minutes after death.

Macroscopic Examination: The distal phalanx of the right index finger was absent. There was a palpable enlargement of the cervical, axillary and inguinal lymph nodes. The hair of the scalp was very scanty.

Large areas of ulceration and excoriation of the skin of the perineum and buttocks were present. A smaller zone occurred on the right arm. The skin had desquamated around the finger-nails.

The heart weighed 160 Gm. (average weight, 85 Gm.).[1] The left and right ventricular walls were markedly thickened, measuring 1.5 cm. and 0.6 cm., respectively. Small scattered atheromatous depositions were observed on the descending aorta.

No abnormalities were present in the lungs.

A gangrenous intussusception was situated in the ileum 120 cm. from Trietz's muscle. The stomach and small bowel above this point were dilated and the bowel below contained blood. The intussusception measured 20 cm. in length and 6 cm. in its greatest diameter. The liver weighed 800 Gm. (average weight, 596 Gm.). On section a normal lobular outline was observed and the parenchyma had a fatty appearance. The spleen weighed 38 Gm. (average weight, 46 Gm.). It was seen to be firm on section with distinguishable malpighian corpuscles and an adherent capsule. The kidneys weighed 70 Gm. each (average weight, 64 Gm.). No abnormalities were present. There were several small discrete zones of hemorrhage in the mucosa of the bladder.

The genital tract appeared normal.

The thyroid, pituitary and suprarenal glands were normal. The thymus was small and weighed 7 Gm.

The spinal fluid had a semigelatinous appearance and was slightly increased in amount. The brain weighed 1120 Gm. (average weight, 1237 Gm.) and showed the normal convolutions and sulci. Grossly, the spinal cord, peripheral nerves, and autonomic nervous system were normal.

Microscopic Examination: The margins of the cutaneous ulcers showed an inflammatory thickening and hyperkeratosis of the epithelium.

A mild reticulo-endothelial hyperplasia of the lymph nodes with poorly defined lymphoid follicles was present.

The muscle fibers of the heart were normal, but there was a slight spreading of the bundles and a slight increase in perivascular fibrosis.

The sections of lung tissue showed a slight terminal hypostatic congestion.

The portion of ileum involved in the intussusception had undergone hemorrhagic necrosis. Fatty vacuolation of the cytoplasm had taken place in the liver cells situated nearest the portal triads. The capsule and trabeculae of the spleen were slightly thickened, and the sinuses prominent. The malpighian corpuscles were diffuse, poorly defined and had undergone slight fibrosis in the center. There was

1. The average weights mentioned in the following report are those given by Coppoletta, J. M., and Wolbach, S. B.: Body Length and Organ Weights of Infants and Children, Am. J. Path. **9**:55 (Jan.) 1933.

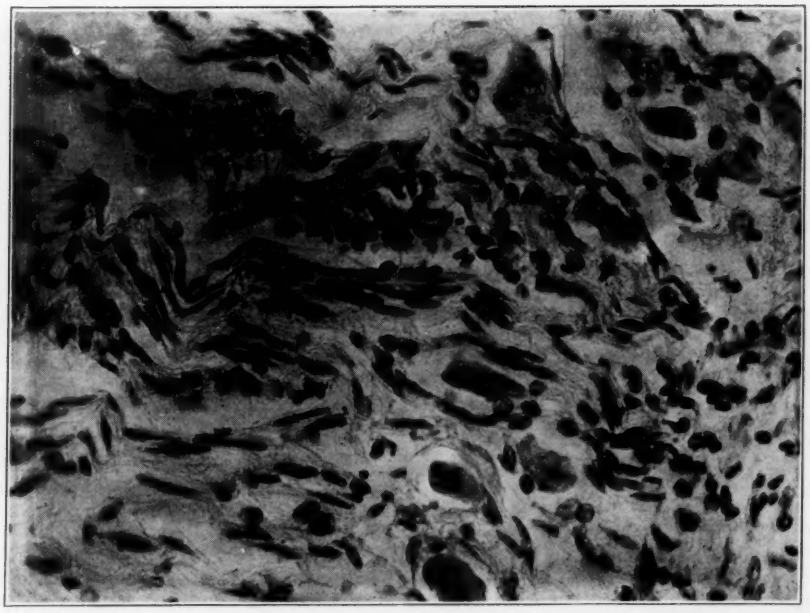

Fig. 3.—Section of the lumbar sympathetic ganglion. Chromatolysis of ganglion cells with focal grouping of mononuclear phagocytic cells.

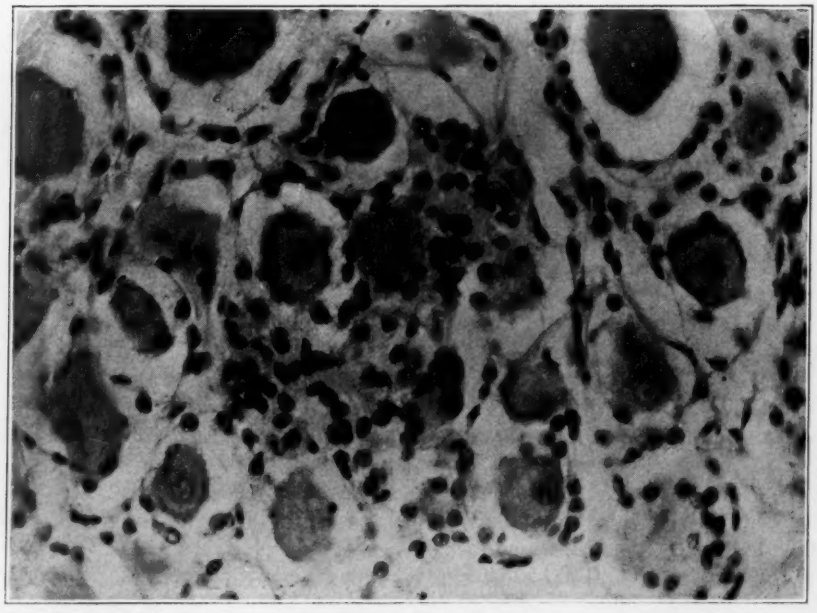

Fig. 4.—Section of a ganglion of a thoracic posterior root. Grouping of mononuclear phagocytic cells around ganglion cells which have undergone chromatolysis and degeneration. Several normal ganglion cells are present.

no evidence of glomerular or vascular changes in the kidneys compatible with hypertension. Scattered lymphocytes in the subepithelial zone of the pelvis indicated a mild chronic pyelitis. Similar collections of lymphocytes were present in the subepithelial zone of the wall of the bladder and in the muscular coat.

The thyroid, pituitary and suprarenal glands were normal. The thymus had undergone the type of involution described as "accidental" by Hammar.

Multiple sections of the cerebrospinal and autonomic nervous systems were stained with hematoxylin and eosin, eosin and methylene blue, phosphotungstic acid and hematoxylin, and by the Pal-Weigert and Marchi methods. There were no distinguishable antemortem changes in the brain or spinal cord. The vagus and sciatic nerves showed a slight spreading of the bundles. Cells of the lumbar sympathetic ganglions and chain had undergone chromatolysis and disappearance of cell outline indicative of neuronophagia. Around some of the cells there was an infiltration of phagocytic cells with the formation of a structure resembling a "rabies tubercle" (fig. 3). A remarkably similar picture was present in the ganglions of the thoracic posterior roots (fig. 4). Examination of the sympathetic ganglions related to the thoracic aorta failed to reveal these changes.

Pathologic Diagnosis.—The following pathologic-anatomic diagnosis was made: (1) early degenerative changes in the ganglions of the lumbar sympathetic chain and posterior roots; (2) hypertrophy of the heart, especially of the left ventricle; (3) chronic nonspecific dermatitis; (4) hyperplasia and degeneration of the lymphoid elements of the spleen and lymph nodes; (5) accidental involution of the thymus gland; (6) chronic pyelitis and cystitis; (7) fatty changes in the liver and (8) gangrenous intussusception of the ileum.

COMMENT

The syndrome of acrodynia is so clearcut that there can be little doubt of the diagnosis in this case. Certain features seem worthy of comment. The high blood pressure is of particular interest inasmuch as, according to Feer,[2] it is of sufficient constancy in acrodynia to be of real value in the differential diagnosis in doubtful cases. A persistently elevated blood pressure is such an unusual finding in the age group in which acrodynia occurs that its presence is extremely significant. The European literature contains many confirmations of Feer's observation,[3] but until Blackfan and McKhann [4] called attention

2. Feer, E.: (*a*) Eine eigenartige Neurose des vegetativen Systems beim Kleinkinde, Jahrb. f. Kinderh. **108**:267, 1925; Ergebn. d. inn. med. u. Kinderh. **24**:100, 1923; (*b*) in von Pfaundler, M., and Schlossmann, A.: Handbuch der Kinderheilkunde, Leipzig, F. C. W. Vogel, 1931, vol. 2, p. 528.

3. (*a*) Railliet, G.: Trois cas d'acrodynie infantile, Rev. franç. de pédiat. **7**: 381, 1931. (*b*) Wyllie, W. G., and Stern, R. O.: Pink Disease: Its Morbid Anatomy, with a Note on Treatment, Arch. Dis. Childhood **6**:137 (June) 1931. (*c*) Wiggelendam, J. M., and Kuiper, T.: Het Ziektebeeld: Acrodynie, Dermato-Polyneuritis, Erythroedema, Vegetativen Neurose (-Ziekte) van Swift-Feer. Nederl. tijdschr. v. geneesk. **2**:250 (July 16) 1927.

4. Blackfan, K., and McKhann, C. F.: Acrodynia; Note on Pathologic Physiology, J. Pediat. **3**:45 (July) 1933.

to it, it has been impossible to find more than an occasional reference to high blood pressure in acrodynia in the American literature. Feer [2b] stated:

> Blood pressure is regularly increased and gives an index to the severity of the infection. The systolic pressure, even at 2 or 3 years of age, rises to 120-140 mm. of mercury, even to 150 mm. and higher. It increases as the disease becomes worse and decreases with improvement. Often the normal is reached only long after clinical recovery and only with severe cachexia, pneumonia or sepsis, does it drop below 100 mm. of mercury.

Another sign to which Feer attached importance in the differential diagnosis of acrodynia is tachycardia, which also persists well into the convalescent period. In our case the pulse rate was never below 120, even during sleep in afebrile periods. It did not slow on vagal pressure or with the administration of atropine. In a case of acrodynia in which there was a heart rate of 164, Wyllie and Stern [3b] demonstrated degenerative changes in the vagus nerve at autopsy, but this could not be found in our case. In spite of hypertension and tachycardia over a period of more than eight months, there was no murmur or other clinical evidence of cardiac insufficiency. At autopsy, as mentioned in the foregoing report, myocardial hypertrophy and slight atheromatous deposits in the descending aorta were observed. Electrocardiograms, taken on Oct. 26, 1931, and Dec. 3, 1931, showed prominent T waves (voltage ranging from 0.4 to 0.48 millivolts) in leads 1 and 2, but none of the other changes reported by Steinbach.[5]

The tone of the skeletal musculature was very poor. Judging from the occurrence of rectal prolapse as well as intussusception in an unusual location, the tone of the intestinal musculature must have been equally poor. Rectal prolapse has been mentioned before in association with acrodynia,[2b] and Paterson and Greenfield [6] have reported one case in which death was likewise due to intussusception.

Autopsy also revealed changes in the liver, thymus, and lymphatic system, which, while not specific, have been reported previously in acrodynia. Warthin,[7] for example, found hyperplasia and degeneration in the lymphatic system and marked atrophy in the thymus in two instances. He also found fatty changes in the liver as did Kernohan

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5. Steinbach, G.: Beitrag zur Kenntnis der Neurose des vegetativen Nervensystems (Feer), Jahrb. f. Kinderh. **136**:208, 1932.

6. Paterson, D., and Greenfield, J. G.: Erythroedema Polyneuritis; So-Called, Pink Disease, Quart. J. Med. **17**:6 (Oct.) 1923.

7. Warthin, A. S.: So-Called Acrodynia or Erythroedema, Arch. Path. **1**:64 (Jan.) 1926.

and Kennedy,[8] Wyllie and Stern [3b] and Davis.[9] The suprarenal and pituitary glands were normal but it is of interest that Woringer [10] and Stolz found hypertrophy in both and that Francioni and Vigi [11] reported enlargement of the suprarenal glands.

As we felt there was much to support the theory that acrodynia is a disease of the nervous system, possibly due to a virus infection, an attempt was made to induce the disease in a monkey. Bilderback, who first described this syndrome in America, has been interested in this possibility. On Dec. 16, 1931, 1 cc. of fresh spinal fluid from the patient was injected intracranially in a monkey. No evidence of an infection appeared. When the patient came to autopsy, a portion of the spinal cord was removed and macerated in a physiologic solution of sodium chloride. This was passed through a Seitz filter, and 2 cc. of the filtrate injected intracranially and 2 cc. intraperitoneally into a monkey. The results were again negative. Studies on guinea-pigs receiving injections of spinal fluid and blood from the patient also gave negative results. Unfortunately, these studies were not made at the beginning of the illness nor at the time when 20 cells were reported in the spinal fluid, but several months later at a time when a virus infection, if present, might well have died out.

The symptomatology of acrodynia would lead one to look for pathologic changes in the nervous system, especially in the sympathetic system. Feer has gone so far as to give the name "neurosis of the vegetative nervous system" to the disease. Autopsy reports, especially recent ones, have contained rather extensive studies of the nervous system and pathologic reports have mentioned degeneration of the myelin sheath of various peripheral nerves,[12] chromatolysis of the anterior horn cells of the spinal cord,[13] and diffuse infiltration of the spinal cord, with small round cells.[14] Cellular changes have also been

8. Kernohan, J. W., and Kennedy, R. L. J.: Acrodynia (So-Called), A Study of the Pathology, Am. J. Dis. Child. **36**:341 (Aug.) 1928.

9. Davis, C. M.: Acrodynia (?), Arch. Pediat. **39**:611 (Sept.) 1922.

10. Woringer, P.: L'acrodynie infantile, Rev. franç. de pédiat. **2**:440, 1926.

11. Francioni, C., and Vigi, F.: Studio di un caso de eritro-edema (acrodinia), Riv. sper. di freniat. **52**:307, 1928; Ancora su di un caso di eritro-edema (acrodinia), rilievi clinici ed istopatologici, Bull. d. sc. med., Bologna **6**:66 (Jan.-Feb.) 1928.

12. (*a*) Wyllie and Stern.[3b] (*b*) Paterson and Greenfield.[6] (*c*) Kernohan and Kennedy.[8] (*d*) Byfield, A. H.: A Polyneuritic Syndrome Resembling Pellagra-Acrodynia (?) Seen in Very Young Children, Am. J. Dis. Child. **20**:347 (Nov.) 1920. (*e*) Bellocq, G. P., and Meyer, R.: Etude clinique et anatomo-pathologique d'une forme grave d'acrodynie, Rev. franç. de pédiat. **8**:495, 1932.

13. Wyllie and Stern.[3b] Paterson and Greenfield.[6] Kernohan and Kennedy.[8] Byfield.[12d]

14. (*a*) Wyllie and Stern.[3b] (*b*) Paterson and Greenfield.[6] (*c*) Findlay, G. M., and Stern, R. O.: A Syndrome in the Rat Resembling Pink Disease in Man, Arch. Dis. Childhood **4**:1, 1929.

described in the lateral [15] and posterior horns [12e] of the spinal cord. In the brain [16] and brain stem [14c] cellular infiltrations have been reported, as well as cellular changes in the infundibulotuberian region [17] and elsewhere. Kernohan and Kennedy [8] reported changes in the ganglion of a posterior root and in the gasserian ganglion. De Lange [16b] called attention to the fact that some of these observations, particularly those reported by Kernohan and Kennedy, may be within normal limits. It is also to be remembered that other changes may be of a secondary nature.

Until the present time, the only report we have been able to find of definite lesions in the autonomic nervous system is that of Bellocq and Meyer,[12e] who reported "numerous foci of neuronophagia and cellular degeneration in the ganglions of the sympathetic chain (cervical and thoracolumbar)." Francioni and Vigi [11] reported lesser changes consisting of a perivascular collar of small round cells in the cervical sympathetic ganglions.[18] Acrodynia followed encephalitis within a short time in their patient. In several other cases [19] the sympathetic nervous system was examined but pathologic changes were not found.

The nervous system was carefully examined in our case. We were unable to distinguish pathologic changes in the numerous sections of the spinal cord and brain or in the vagus, sciatic or recurrent laryngeal nerves. The slight spreading of the nerve bundles of the vagus and sciatic nerves was not considered evidence of a definite antemortem lesion. In the autonomic nervous system, however, sections of the lumbar ganglions showed that many of the ganglion cells had undergone a loss of cell outline and chromatolysis. In many places these ganglion cells were surrounded by phagocytic cells (fig. 3). A similar picture of chromatolysis and infiltration with phagocytes was seen in the ganglions of the thoracic posterior roots (fig. 4). Comparison of the latter sections with corresponding ones from a normal child of 5 years failed to reveal in the normal sections any cells which gave a picture resembling chromatolysis. According to de Lange, however, a picture suggesting chromatolysis may occur normally in the ganglions of the posterior roots and certain other regions of the nervous system.

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15. Orton, S. T., and Bender, L.: Lesions in the Lateral Horns of the Spinal Cord in Acrodynia, Pellagra, and Pernicious Anemia, Bull. Neurol. Inst. New York **1**:506 (Nov.) 1931.

16. (*a*) Wyllie and Stern.[3b] (*b*) de Lange, C.: Zur mikroskopischen Anatomie des Zentralnervensystems bei Pink Disease, Jahrb. f. Kinderh. **136**:193, 1932.

17. Francioni and Vigi.[11] Bellocq and Meyer.[12e] de Lange.[16b]

18. Apparently an error occurs in the article by Bellocq and Meyer, in that they stated that Francioni and Vigi found the sympathetic ganglions normal. Such was not the case.

19. Wyllie and Stern.[3b] Blackfan and McKhann.[4] Paterson and Greenfield.[6] Findlay and Stern.[14c]

We feel that the presence of an infiltration of small round cells in our sections confirms the pathologic nature of our observations.

SUMMARY

1. A case of acrodynia is reported and attention is called to the significance of high blood pressure and tachycardia in the disease.

2. An unsuccessful attempt was made to induce the disease in a monkey by intracranial inoculation with the patient's spinal fluid and with a filtrate of the spinal cord.

3. Pathologic changes in the sympathetic nervous system and in the ganglions of the posterior roots are reported. Somewhat similar changes have been reported in acrodynia by other investigators.

NOTE.—Since submitting this report, two interesting articles on acrodynia have appeared in American pediatric journals. Cobb (AM. J. DIS. CHILD. **46:** 1076 [Nov.] 1933) reported four new cases with hypertension and tachycardia, and Wolf, Paterson and Davison (*J. Pediat.* **4:** 498 [April] 1934) one with changes in the brain, spinal cord and peripheral nerves seen at autopsy. No mention was made of the sympathetic system. In discussing previous pathologic reports, both authors have apparently overlooked the changes in the sympathetic system noted by Bellocq and Meyer, and by Francioni and Vigi.

Miss Beatrice Howitt of the Hooper Foundation for Medical Research cooperated in attempting animal inoculation.

Progress in Pediatrics

KALA-AZAR IN CHILDREN

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Kala-azar is rare in the United States. Only 3 cases in children have thus far been reported in the American literature.

The first case in this country was recorded by Talbot and Lyons [1] in 1918. Their patient was a Greek child who presented the classic symptoms. Nonspecific treatment, including administration of iron, was tried without success. Transfusion was given, and splenectomy was performed. Temporary improvement followed. Finally antimony and potassium tartrate was given intravenously, with marked improvement in the general condition and relief of specific symptoms.

In 1922, Faber and Schussler [2] reported a case of systemic leishmaniasis in a child of 3 years. The patient came from Italy about six months before the onset of the illness. Following the establishment of the diagnosis, intravenous injections of antimony and potassium tartrate were given with satisfactory results.

In 1925, Wollstein [3] reported the third case. The patient was a child, aged 21 months, born in Sicily. Noma had developed, and the child's condition became poor. Although intravenous injections of a solution of antimony and potassium tartrate were begun and two transfusions were given, the child died within two weeks after admission, before a significant dosage could be administered. It is of additional interest that antemortem examination revealed Leishman-Donovan bodies in the bone marrow, and on postmortem examination Leishman-Donovan bodies were found in sections from the spleen, liver and kidney. Wollstein stated the belief that the cause of death was noma, not kala-azar.

The only other report of systemic kala-azar recorded in this country is that of Junkin,[4] who described the disease in a male Indian, aged 22,

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From the Pediatric Service of Dr. Béla Schick, Mount Sinai Hospital.

1. Talbot, F., and Lyons, A. B.: Kala-Azar in Child, Am. J. Dis. Child. **16**:154 (Sept.) 1918.

2. Faber, H. K., and Schussler, H.: Leishmaniasis in the United States, J. A. M. A. **80**:93 (Jan. 13) 1923.

3. Wollstein, M.: New York State J. Med. **25**:413, 1925.

4. Junkin, C. I.: Kala-Azar; Case Occurring in New York, J. A. M. A. **86**: 479 (Feb. 13) 1926.

who came from Calcutta. The condition was noted during observation for an intra-abdominal injury sustained as the result of a fall. The patient was treated with antimony and potassium tartrate, but treatment was frequently interrupted because of intolerance for the drug. The author felt, however, that in the eleven months during which the patient was under observation his condition showed little downward progress. Strictly speaking, Junkin's case does not fall within the scope of this paper. It belongs rather to the Indian form of kala-azar, which though pathologically and symptomatically identical in most respects, still presents certain peculiar epidemiological differences, which to many observers warrant its separate consideration. For the purpose of clarity, the discussion in this paper will be limited to the infantile or Mediterranean form of kala-azar.

The case to be described here constitutes the fourth case of systemic kala-azar in children recorded in this country. It will be noted in the tabular analysis of the 4 cases (table 1) that each of the patients came from endemic centers, and that each patient was in this country a minimum of two and one-half months before the onset of the illness. Antimony and potassium tartrate was administered at some point in the course of treatment in each case.

The long and variable period of incubation which characterizes kala-azar makes the condition difficult of detection at the time the patient enters this country; yet when the disease runs a characteristic course, the diagnosis is not difficult. Treatment, when instituted early and pursued thoroughly, gives satisfactory results.

A review of a case with successful treatment in the children's ward of the Mount Sinai Hospital and a survey of the literature may help emphasize the important epidemiological, clinical and therapeutic features.

REPORT OF A CASE

Our patient, E. C., was a Greek boy, aged 5½ years, who had arrived from Greece fourteen months prior to his admission to the Mount Sinai Hospital. He entered the children's service on Jan. 7, 1932, with a history of having had an attack of measles five months previously, from which he convalesced slowly and which had left him weak. One month after this episode, during an attack of grip, the abdomen was first observed to be enlarged. Following the subsidence of the acute attack, the abdomen continued to enlarge gradually, and a low grade fever ranging from 99 to 101 F. persisted. Pallor and weakness became marked. Walking or exercise quickly provoked shortness of breath, so that the boy preferred to lie in bed all day. There was loss of weight, although the appetite remained good. The urine became dark; the stools were normal. The child had had no chills or rash. Sweating was profuse. The symptoms continued, and the abdomen became progressively more swollen. Four days before admission the boy had a sudden rise in temperature to about 103 or 104 F.; he was brought to the hospital because of this.

TABLE 1.—*Analysis of Four Cases of Infantile Kala-Azar Reported to Date in the American Literature*

Author	Year Reported	Age	Sex	Nativity	Arrival in U. S. A. Before Hospitalization	Known Duration of Illness	Therapy	Comments
Talbot and Lyon [1]...	1918	4 years	Female	Greece	8 months	7 months	Intravenous injection of 2 per cent solution of antimony and potassium tartrate; 0.02 Gm. increased gradually to 0.08 daily, later alternate days for one month; total dose not recorded	In hospital three months; cured; seen one year later, apparently cured
Faber and Schussler [2]	1923	27½ months	Female	Italy	11 months	5 months	Intravenous injection of 2 per cent solution of antimony and potassium tartrate twice a week; dose of 10 mg. increased gradually to 100; total amount 27½ grains (1.76 Gm.) in thirty-three injections over a period of three months	In hospital three months; seen one month later, apparently cured
Wollstein [3].....	1925	21 months	Male	Sicily	2½ months	3¾ months	Intravenous injection of 1 per cent solution of antimony and potassium tartrate; dose 4 cc. frequently repeated over a period of two weeks; total dose not reported	Noma had developed before therapy started; death from noma in two weeks
Ginandes.....	1934	5½ years	Male	Greece	14 months	6 months	Intravenous injection of antimony and potassium tartrate in 5 cc. of saline solution; doses 0.004 Gm. (1/16 grain) increased by like amount every four days; total amount 1.733 Gm. (26 grains) over a period of six months	In hospital nine and one-half months; seen one year later; child cured

The past history was essentially negative. The child had had an infestation with round worms at the age of 3, which subsequently cleared up. He had had an attack of bronchopneumonia at 3½ years. There was a tonsillectomy ten months before admission, and five months later, he had the attack of measles. The physician who treated the child for measles did not note unusual pallor or prominence of the abdomen.

The developmental history was essentially normal.

The family history was irrelevant. The parents and three sisters were well. There was no history of a similar ailment in the immediate family, although an uncle had had kala-azar in Greece many years earlier. The father had had malaria thirty-five years before, from which he had completely recovered.

Fig. 1.—*A*, the patient prior to treatment. Note the size of the spleen and the liver and the poor nutritional state. The dressing covers the site of the sternal (bone marrow) puncture. *B*, the patient three months after the completed course of treatment with antimony and potassium tartrate ready for discharge from the hospital. The decrease in the size of the liver and the spleen and the improved nutritional state are apparent. *C*, the patient one year after the treatment was instituted. The spleen is further decreased in size. The nutritional status is good.

In summary, then, this Greek boy was brought into the hospital with a history of progressively increasing pallor, loss of weight, asthenia, fever and increasing swelling of the abdomen of four months' duration.

On admission, the child appeared chronically ill, apathetic and listless (fig. 1 *A*). The eyes were sunken, the skin was sallow, and the mucous membranes pale. The muscle tone was poor. The abdomen was markedly protuberant, the child assuming a rearing-back position. The entire left half of the abdomen, from the costal margin down to 2 fingerbreadths above Poupart's ligament and extending over to the right border of the right rectus muscle, was filled by an enlarged, firm, some-

TABLE 2.—*Essential Data During the Course of a Case of Infantile Kala-Azar*

Date	Intravenous Dose of Antimony and Potassium Tartrate: Grains	Intravenous Dose of Antimony and Potassium Tartrate: Grams (approx.)	Hemoglobin (Sahli) per Cent	Red Cell Count	Character of Red Cells	Differential Count: White Cell Count	Differential Count: Polymorphonuclears: Segmented, per Cent	Differential Count: Polymorphonuclears: Non-segmented, per Cent	Differential Count: Lymphocytes, per Cent	Differential Count: Monocytes, per Cent	Differential Count: Other Cells	Size* of Spleen, Cm.
1/ 7/32	No treatment		34	3,300,000	Poikilocytosis, anisocytosis, polychromatosis, central achromia	3,400	20	8	60	7	3% plasma 2% myelocytes	18
1/ 9/32	No treatment		44	3,220,000	Marked anisocytosis, poikilocytosis, basophils	2,300	25½	2½	67	2½	2.5% plasma 1.8% reticulocytes	
1/23/32	Treatment begun 1/16	0.004	44	.....	.....	2,450	26	..	63	9	1% blasts 1% basophils	
1/26/32	1/8	0.0075	44									
1/30/32†	3/16	0.012†	44	3,150,000	.....	3,900	22	..	66	8	4% blasts	16
2/ 3/32†	1/8	0.0075	48	3,630,000	Moderate anisocytosis, poikilocytosis, polychromatosis	3,400	32	4	50	14	.....	15.5
2/ 7/32†	3/16	0.012	52	3,640,000	.....	3,000	24	6	50	8	2% eosinophils 2% basophils 4% metamyelocytes 2% myelocytes 1% plasma 1% macrophages	15.5
2/11/32†	1/4	0.015	50	3,110,000	Moderate polychromatosis	2,500	26	4	58	8	2% metamyelocytes 2% myelocytes	
2/15/32†	1/4	0.015	52	3,150,000	Moderate anisocytosis, 3% of nucleated red blood cells	2,450	14	..	75	6	5% blasts	
2/19/32	1/4	0.015										
2/23/32	5/16	0.019										
2/27/32	5/16	0.019	48	.....	Stippled red blood cells	2,200	18	..	76	4		
3/ 2/32	5/16	0.019	48	3,200,000	.....	3,100	33	..	62	5		
3/ 7/32	5/16	0.019	46	.....	.....	.....	..	..	..	..	.....	22
3/12/32	3/8	0.024	52	.....	.....	.....	.	..	..	..	.. ..	22
3/17/32	3/8	0.024										
3/22/32	3/8	0.024	46	3,250,000	.....	4,050	25	..	65	4	4% blasts 2% myelocytes	

3/26/32	1/2	0.035										
3/31/32	1/2	0.035	..	.....	.....	.....	..	..	..	..	.....	18
4/ 5/32	...	0.035	50	.....	.....	2,500	..	..	..	..	.....	18
4/10/32	...	0.035	50	.....	.....	3,000	..	..	..	..	.....	19
4/14/32	3/4	0.045										
4/19/32	...	0.045	46	.....	.....	3,000	..	..	..	..	.....	19
4/23/32	...	0.045	52	.....	.....	3,800	32	..	62	6	.....	20
4/27/32	...	0.045	56	3,240,000	.....	3,400	34	..	62	..	4% eosinophils	
5/ 3/32†	7/8	0.0525	42	.....	.....	4,000	23	4	48	21	4% macrophages	
5/11/32	1	0.06‡	46	3,800,000	.....	5,900	34	..	50	16		
5/18/32	3/4	0.045	50	.....	.....	6,800	50	..	36	14		
5/24/32	1	0.06	70	3,400,000	.....	7,600	44	..	52	4	.....	20
5/30/32	...	0.06										
6/ 3/32	...	0.06	57	3,520,000	.....	5,200	30	..	70	..	.....	18.5
6/ 7/32	...	0.06										
6/11/32	...	0.06	60	.....	.....	.....	..	..	..	..	.....	18.5
6/15/32	...	0.06										
6/19/32	...	0.06	54	3,420,000	.....	5,600	42	..	58			
6/25/32	...	0.06	54	.....	.....	.....	..	..	..	..	.....	18
6/29/32	...	0.06	54									
7/ 3/32	...	0.06	42	3,400,000	.....	3,600	65	..	30	5		
7/10/32	...	0.06										
7/14/32	...	0.06										
7/18/32	...	0.06										
7/22/32	...	0.06	45	3,650,000	.....	3,650	68	..	24	8		
7/27/32	...	0.06	52	3,290,000	.....	5,850	30	..	52	10	5.6% reticulocytes 3% eosinophils 3% blasts 1% myelocytes	18
	Treatment ended											
9/ 6/32	No treatment		82	4,690,000	.....	9,800	37	..	59	1	2% eosinophils 1% basophils	
10/11/32	No treatment		78	4,800,000	.....	9,100	53	..	34	10	2% eosinophils 1% basophils	10
12/15/32	.....		..	.....	.....	.....	..	..	..	..	.....	6 below C.M.
12/20/32	.....		..	.....	.....	.....	..	..	..	..	.....	3
1/27/33	.....		84	4,210,000	.....	7,200	40	18	36	4	2% blasts	6
4/20/33	.....		..	.....	.....	.....	..	..	..	..	.....	3
7/20/33	.....		84	4,800,000	.....	9,400	63	..	30	5	2% eosinophils 2% myelocytes 1% basophils	3
1/18/34	.....		..	.....	.....	.....	..	..	..	..	.....	3

* The spleen was measured in the midline from the tip of the xiphoid to the notch in the inferior border of the spleen. After the first discharge from the hospital, the figures for the size of the spleen refer to the distance below the costal margin.

† The figures for the blood on these dates were taken from tests made on the following day.

‡ Diarrhea and vomiting set in; hence the succeeding dose had to be reduced.

what movable spleen, the edge of which could be clearly outlined. The liver was 3 fingerbreadths below the costal margin. There was no edema, pigmentation or unusual adenopathy. The rest of the physical findings were of no consequence.

The tuberculin, Wassermann and Kahn tests were negative. The urine was repeatedly normal. The blood pressure was 114 systolic and 91 diastolic. An x-ray picture of the extremities showed no unusual rarefaction and no periosteal changes.

The blood on admission revealed a hemoglobin of 34 per cent (Sahli). The red cell count was 3,300,000, the cells showing marked anisocytosis, poikilocytosis and polychromatophilia. The white cell count was 3,400, of which 30 per cent were polymorphonuclear cells, 60 per cent lymphocytes and 10 per cent monocytes. No malarial or other parasites were seen on smear. The platelet count was 130,000; there were 1.2 per cent reticulocytes. A sedimentation test performed while the patient was under treatment showed an accelerated rate of sedimentation. This is in agreement with the findings of Napier and Henderson.[5]

The blood chemistry was normal, except that the total cholesterol was 130 mg. per hundred cubic centimeters, with only a faint trace of the ester present, which during the course of treatment rose to 41 mg. This coincides with the findings of Garcia [6] subsequently referred to. Studies of the bile pigment in the blood revealed a normal icteric index; the van den Bergh test was normal, both direct (negative) and indirect (1: 500,000 equals 0.2 mg.). The stool contained no evidence of parasites or of blood. Quantitative measurement showed an increased excretion of urobilin (720 mg. in a seventy-two hour specimen). Bleeding time and coagulation time were normal. The total amount of protein in the blood was normal on admission, but the partition showed a marked increase in the globulin; thus the albumin was 3.7 Gm. and the globulin 3.7 Gm. per hundred cubic centimeters. The increase in the globulin persisted, showing only slight variations on repeated examinations. This is a common finding in kala-azar.[7]

Numerous diagnoses were considered to account for the splenomegaly and the anemia, such as malaria, leukemia, Gaucher's disease, von Jaksch's anemia and Cooley's anemia. The origin of the patient, however, the history of the illness and the size and consistency of the spleen suggested a tentative diagnosis of kala-azar. The diagnosis was verified by puncture of the bone marrow, a smear of which was reported by Dr. Freund, hematologist in the pediatric service, to contain numerous intracellular parasites. Culture of bone marrow on N. N. N. mediums yielded the motile leptomonas form. The aldehyde (dilute formaldehyde-gel) test of Napier and the Sia modification of the Ray hemolytic test (both of which are described later) gave further confirmatory evidence. These tests were also performed on the child's parents, with negative results. It may be noted here that the spleen could not be palpated in either parent.

The diagnosis having been verified, treatment was begun under the supervision of Dr. F. W. O'Connor, who has had considerable experience with this form of therapy. Antimony and potassium tartrate (0.004 Gm. [1/16 grain]) in 5 cc. of saline solution was administered intravenously, and this dose was increased by a similar amount every four days. Twice during the treatment the patient manifested toxic symptoms such as vomiting, fever and abdominal cramps, which necessitated reducing the succeeding dose of the drug.

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5. Napier, L. E., and Henderson, J. M.: Indian J. M. Research **19**:691, 1931.
6. Garcia, P. M.: An. de med. int. **1**:705, 1923.
7. Lloyd, R. B., and Paul, S. N.: Indian J. M. Research **16**:203, 1928.

The reaction to treatment was dramatic. As early as the second week there was a marked improvement which, except for rare intervals, continued during the entire stay in the hospital. Table 2 gives the essential data on the course of the disease.

In the first three months the hemoglobin rose to 52 per cent. The red blood cell count varied between 3,000,000 and 4,000,000. The white cell count remained between 3,000 and 4,000, with a persistent relative lymphocytosis.

The temperature at first presented the typical double remission in twenty-four hours, rising to an average daily height of 103 F. (fig. 2). During the third month the level became lower, and the double remissions were absent.

The spleen presented considerable variation in size; at times it receded and at times it became enlarged in the presence of intercurrent infection with fever. The injection of 5 minims (0.3 cc.) of epinephrine hydrochloride caused a shrinkage of 2.5 cm. within five minutes. At the end of three months the spleen was only slightly smaller than on admission.

At this time acute submaxillary adenitis developed. The temperature rose to 104 F. Coincidentally there was a marked enlargement of the spleen, which extended

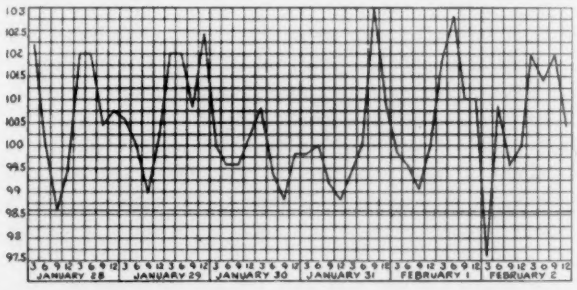

Fig. 2.—Temperature curve over a period of six days in a case of infantile kala-azar, showing the marked irregularity and the characteristic double rise in twenty-four hours.

down to 22 cm. below the xiphoid in the midline. The boy was then receiving 0.019 Gm. (5/16 grain) of antimony and potassium tartrate every four days. Treatment was continued uninterruptedly. The question arose as to whether the swollen submaxillary gland and its subsequent breakdown were due to infection or to a toxic effect of the drug, the latter possibility having been reported in the literature. The child's teeth and tonsils were apparently free from infection. Roentgen and local examination revealed that the jaw was not involved. The swelling became soft and fluctuant. It was incised. The temperature dropped shortly after the incision. Culture of the pus yielded Streptococcus haemolyticus and was negative for Leishman-Donovan bodies. During the acute infection and for one week after drainage was established, the spleen remained unchanged in size. After this, it showed only a slow recession. The abscess continued to drain for about one month, but recovery was eventually complete. In spite of this acute episode, the general condition of the child showed improvement; the hemoglobin remained about 50 per cent; the white cells showed no marked change in the total or the differential count.

During the fourth month the patient had a severe acute infection of the upper respiratory tract from which he recovered promptly. About two weeks later there

was a sharp rise in temperature to 105 F., and signs of pleuropneumonia were apparent at the base of the left lung. The patient appeared toxic, cyanotic and critically ill. The hemoglobin was 50 per cent, the red cell count, 3,800,000, and the white cell count showed a definite rise to 6,800, with 50 per cent polymorphonuclear cells, 36 per cent lymphocytes and 14 per cent monocytes. The spleen was enlarged to 20 cm. below the costal margin. A transfusion was given, and the usual symptomatic treatment instituted, but the administration of antimony and potassium tartrate was not interrupted. Within a week the temperature dropped to normal and remained normal, even though the signs in the chest were somewhat slower in resolving. Following this infection, the temperature remained normal for about a month, not even showing the previous daily peaks so characteristic of kala-azar. The spleen decreased slowly in size. The hemoglobin remained between 50 and 60 per cent, the red cell count between 4,000,000 and 4,500,000 and the white cell count between 5,000 and 6,000.

During the latter part of the seventh month in the hospital, low grade irregular fever without apparent cause developed. The white cell count dropped to between 3,000 and 4,000 with 65 per cent polymorhonuclear cells, 30 per cent lymphocytes and 5 per cent monocytes. Although search was made for evidence of acute infection to account for the unusual rise in temperature and increase in polymorphonuclear cells, no satisfactory cause was found. The assumption was therefore that the Leishmania infection was still active. The temperature fluctuated between 99 and 100.5 F. for about two weeks; then it became normal.

Treatment was discontinued two weeks thereafter (July 27). In the six and one-half months of active treatment the boy had received a total of 1.733 Gm. (26 grains) of antimony and potassium tartrate. The administration of the drug had been uninterrupted throughout the course of the numerous intercurrent infections. The general supportive measures familiar to hospital routine and a diet high in calories, containing 100 Gm. of liver daily, were given throughout.

The total stay in the hospital was nine and one-half months. During the last three months the course was uneventful. The patient continued to improve. Apparently the persistent therapy was exerting its most favorable action during these three months after cessation of treatment. The spleen, which was 18 cm. when treatment was stopped, slowly decreased in size until it measured about 10 cm. on discharge. The temperature remained normal except for an occasional and insignificant rise. The listlessness and apathy of the child had entirely disappeared. The muscle tone was excellent. Strength was improved. The abdomen was less protuberant. The child ate well and gained steadily, so that on discharge he weighed 21,250 Gm., a gain of 4,000 Gm. over his weight on admission. Most of this gain occurred during the last three months, a period when the disease had become relatively inactive. The hemoglobin steadily increased to 78 per cent, with a red cell count of 4,800,000. The white cells rose to a normal level of 9,100, with 53 per cent polymorphonuclear cells, 34 per cent lymphocytes, 10 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The red cells at this time showed no abnormal characteristics in size, shape or staining reaction. The aldehyde (dilute formaldehyde-gel) test and the modified hemolytic test, although still positive, showed a markedly diminished intensity of reaction.

The boy was discharged (fig. 1 *B*) on October 18 and was later seen in the follow-up clinic. In December 1932, two months after his discharge, his general condition was excellent. He was fever-free. The spleen had decreased to 3 cm. below the costal margin, and appeared to be much softer than on previous examinations. The child was alert and active. In the interim, he had sustained an extensive laceration of the thigh due to a dog's bite which had healed well after cauterization.

In January 1933 the child was readmitted to the hospital (fig. 1 *C*) because of an attack of acute bronchopneumonia. On this admission the spleen was somewhat larger (6 cm.), probably in response to the acute infection, since the child had manifested no signs of activity of the kala-azar infection after he left the hospital. The hemoglobin was 84 per cent; the red cell count, 4,210,000, and the white cell count, 7,200, with 58 per cent polymorphonuclear cells, of which 18 per cent were staff cells and 40 per cent segmented forms. There were 36 per cent lymphocytes, 2 per cent young blast forms and 4 per cent monocytes. The recovery from the pneumonia this time was rapid. Within two weeks the boy was discharged in excellent condition.

In April 1933 the child was again seen at the follow-up clinic. His general condition was satisfactory. The spleen was only 3 cm. below the costal margin.

On his visit to the clinic on July 20, approximately one year after the course of treatment was discontinued, the child's condition was excellent. He was then 7 years old. He had gained weight steadily so that he weighed 25,500 Gm. He had grown 11 cm. in height since his first admission to the hospital. He was symptom-free. His spleen was still enlarged to 3 cm. below the costal margin. The modified hemolytic test (Sia) and the aldehyde (dilute formaldehyde-gel) test gave negative results. The hemoglobin was 84 per cent, the red cells numbering 4,800,000 and the white cells 9,400, with 63 per cent polymorphonuclear cells, 30 per cent lymphocytes, 2 per cent eosinophils, 5 per cent monocytes, 2 per cent myelocytes and 1 per cent basophils.

The patient was last seen on Jan. 18, 1934. The spleen was still 3 cm. below the costal margin. The edge of the liver was barely palpable. The general condition was excellent.

COMMENT

Although numerous diagnoses suggested themselves in this case, the true condition was suspected early, and it was fortunate that the diagnosis was verified by positive culture and smear of the bone marrow, as well as by corroborative serum tests. The ease of puncture of the bone marrow as a means of diagnosis should be emphasized. It is a procedure which for the inexperienced practitioner is simple and fraught with far less danger than is puncture of the spleen.

One appreciates the importance of antimony and potassium tartrate as a therapeutic contribution when one is able to trace the progress of a case of kala-azar under this treatment. The significant improvement in the development and the nutrition of the patient following treatment is worth noting. The course of therapy lasted more than six months, a period which is longer than that given in the cases previously cited in the American literature. It is possible that inexperience prompted overcaution, and that larger doses might have been used. It was thought preferable, however, to err on this side rather than run the risk of untoward results. Even with these small doses, the patient occasionally reacted unfavorably, and the succeeding dose had to be decreased.

Taking into consideration the conservative treatment, the response was slower than might have been expected. The spleen decreased slowly during the active stage of the disease. This was contrary to

the numerous reports in the literature emphasizing the rapid shrinking of the spleen under treatment. Because of this slow response, the advisability of changing to another antimony preparation was discussed. This has frequently been suggested in the literature. The discouragement which my associate and I felt was fortunately tempered by the counsel of Dr. O'Connor, who felt that the favorable general reaction of the child was a hopeful sign and therefore urged the continuance of the slow therapy.

The decrease in the size of the spleen following the cessation of therapy was more pronounced. It is likely that the antimony and potassium tartrate was then exerting its maximum action. Within a period of about three months after treatment was discontinued the spleen decreased about 8 cm. in size, whereas during the entire course of treatment it had been only slightly influenced. This slowness of response may have been attributable to the frequent intercurrent infections. In fact, during the attack of acute cervical adenitis, the spleen increased about 6.5 cm., even though treatment with antimony and potassium tartrate was uninterrupted. When the child was last seen, at a time when he had been free from evidence of activity of the disease for about a year, the spleen was still enlarged to about 3 cm. below the costal margin. The cause of this enlargement was not clear. Considering that the patient had entered this country fourteen months previous to admission, and that the period of incubation may be as long as from three to six months, it may be assumed that the disease was active for from eight to eleven months before the child was hospitalized. It is possible that the chronicity of the process prior to the institution of therapy had induced a moderate fibrosis of the spleen, making its complete recession difficult.

The response of the bone marrow was similarly slow. Although there was a slight increase in the total leukocyte count from about 3,000 on admission to from 5,000 to 6,000 at the end of treatment, the ratio of the polymorphonuclear cells to the lymphocytes was in the main unchanged. Following cessation of treatment, the ratio tended to become more normal, and when the child was last seen, the ratio had become altogether normal.

The response of the leukocytes to acute intercurrent infections early in the course was not striking. During the acute submaxillary adenitis, the total count rose to only about 3,800 without any marked change in the differential count. Later, during the acute pulmonary infection, when the total dose of antimony and potassium tartrate administered had become more significant, there was a rise in the total count to about 8,000, with a rise in the polymorphonuclears to 44 per cent. It is recognized that the nature of the infection may have played a rôle in the leukocytic response.

As occurred with the spleen and the leukocytes, the red cells also showed significant changes only after the total dose had been administered. It is of interest that basophilic stippling of the red cells appeared early in the course of treatment. Talbot and others reported similar changes during the course of therapy.

The hemoglobin, though showing an early and fairly steady rise during the course of treatment, likewise made more rapid gains only after the complete dose had been given.

This delayed response of the entire hemopoietic system may mean that the total dose was essential before marked improvement was possible. Of course, the exhausting influence of the repeated intercurrent infections may have to some degree interfered with the effectiveness of therapy. This is difficult to evaluate.

One cannot emphasize too strongly the need for uninterrupted treatment. This is the most important phase of the therapy, although the prevention of intercurrent infections and the maintenance of adequate nutrition through a diet high in calories are invaluable adjuvants.

The insidious beginning of kala-azar and the variable period of incubation make the task of the immigration officer difficult. That the diagnosis must be suspected, more especially in children coming from endemic centers, cannot be too greatly stressed. It is likely that with a better understanding of the condition the disease will be diagnosed more frequently than heretofore.

REVIEW OF THE LITERATURE

History of Kala-Azar.—Kala-azar (black fever) has been variously referred to in the literature. Prior to the identification of the etiologic agent, the clinical picture of fever, splenomegaly, anemia and cachexia took its name from the locality in which it appeared. "Tropical febrile splenomegaly," "Assam fever," "dum-dum fever," "Burdwan fever" and "kala-dunkh" or "kala-dukh" are some of the designations used in India. In the literature of the last two decades of the nineteenth century, the disease was linked with malarial cachexia, Malta fever, dysentery, ancylostomiasis and various combinations of these diseases. After 1903, when the parasite was discovered, the segregation of the disease entity became complete, and the various local names to some extent gave way to the more commonly accepted designation "kala-azar."

The parasites causing kala-azar were frequently referred to by numerous observers before Leishman's paper appeared. It remained, however, for Leishman,[8] in 1903, to demonstrate the organism in smears from the spleen of a soldier from Dum Dum, India, who had died of tropical splenomegaly three years before. Leishman believed that the

8. Leishman, W. B.: Brit. M. J. **1**:1252, 1903; **2**:1376, 1903.

parasite found was a degenerate trypanosome. Working independently in the same year, Donovan [9] confirmed Leishman's discovery by finding similar bodies in the spleens of patients dying from prolonged fever in Madras and in fresh blood obtained by puncture of the spleen in a living patient affected with tropical splenomegaly. Confirmation of these observations by numerous observers was rapid. Ross [10] subsequently gave the name "Leishmania Donovani" to the parasites.

One year after the discovery of the parasites, Rogers [11] demonstrated that by the addition of splenic pulp from infected patients to saline solution containing sodium citrate, the sporelike forms would develop into flagellates. Although Wright,[12] as early as 1903, showed that oriental sore was due to Leishmania, Nicolle,[13] in 1908, obtained cultures of Leishmania from patients with oriental sore and thus demonstrated the close relationship between this condition and kala-azar.

In appreciation of the wide distribution of leishmaniasis, attempts were made to identify the numerous strains of the organism, either by geographic distribution or by biologic characteristics. Thus, in 1931, Adler and Theodore [14] listed seven species of Leishmania that had been studied experimentally in sandflies. The most common species recognized are those found in man, namely, Leishmania infantum, which is responsible for the Mediterranean form of kala-azar; Leishmania Donovani, responsible for the Indian form of kala-azar; Leishmania tropica, the cause of oriental sore, and Leishmania braziliensis, the cause of a generalized cutaneous form of leishmaniasis found in southern and central America.

It has further been demonstrated that dogs which have been naturally infected with these various strains manifest a visceral and cutaneous form of leishmaniasis. Other vertebrates have also been suggested as natural hosts, but there is still some question as to the exact identity of the parasites found in these animals.

Characteristics of the Parasite.—In man and in the dog the Leishmania parasite is almost invariably found in the round or oval stage, although the flagellate form is reported to have been observed in one or two isolated instances. The parasite in its typical form is a small organism usually circular or oval in outline. It consists of a mass of cytoplasm containing two characteristic structures: a spherical nucleus about two-thirds of the diameter of the organism, which is applied to one of the

9. Donovan, C.: Brit. M. J. **2**:79, 1903.
10. Ross, R.: Brit. M. J. **2**:1261 and 1401, 1903.
11. Rogers, L.: Lancet **2**:215, 1904.
12. Wright, J. H.: J. M. Research **5**:472, 1903.
13. Nicolle, C.: Compt. rend. Acad. d. sc. **146**:842, 1908.
14. Adler, S., and Theodore, O.: Investigations of Medical Kala Azar, Proc. Roy. Soc. London, s.B **108**:447, 453, 481 and 495, 1931.

flatter sides of the cell; and a kinetoplast, a rodlike structure which usually lies with its long axis directed toward the nucleus. On careful staining by the Romanowsky method or a modification of it,[15] a thread-like line can be traced from the kinetoplast to the surface of the parasite. This is the axoneme, which in the flagellate form gives rise to the flagellum. The size of the parasite varies considerably. When it is spherical, it measures from 1 to 3 microns in diameter. More usually it is ovoid (fig. 3).

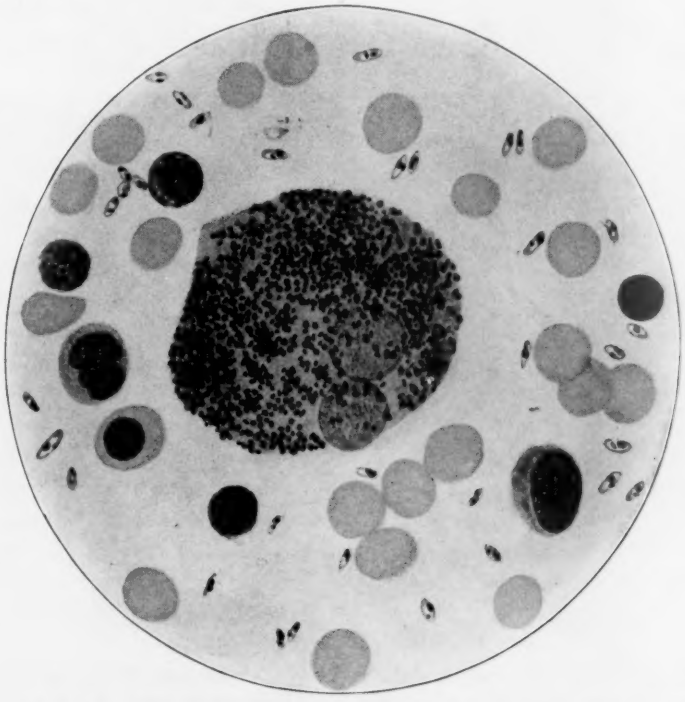

Fig. 3.—Smear of juice from the spleen obtained by puncture. Note the large endothelial cell loaded with parasites. Extracellular parasites and elements from the blood and spleen are present. An axoneme is not here visible. Leishman's stain was used. (Photograph after Jemma.[19])

Culture of the parasite is easily accomplished on Locke blood agar, in McNeal's rabbit blood agar and in a simplified medium known as the N.N.N. (Novy, McNeal and Nicolle[16]). In this medium subculture can easily be obtained. Active flagellate forms (fig. 4) may be seen in cultures from forty-eight to seventy-two hours after the medium has been inoculated with heavily infected material.

15. Maurer, G.: Centralbl. f. Bakt. **32**:695, 1903.
16. Nicolle, C.: Bull. Soc. path. exot. **1**:121, 1908.

Attempts to differentiate the various species of Leishmania on a morphologic basis have not been successful. Wenyon [17] pointed out that Leishmania Donovani, which produces a generalized infection in man, may give rise to purely cutaneous lesions in animals (as also occasionally in man); while Leishmania tropica, which causes local cutaneous lesions in man, may produce a generalized infection in animals.

The serologic tests usually employed to differentiate species have not been entirely successful either in man or in the dog. In 1924, Noguchi [18] demonstrated that serologically Leishmania fall into three

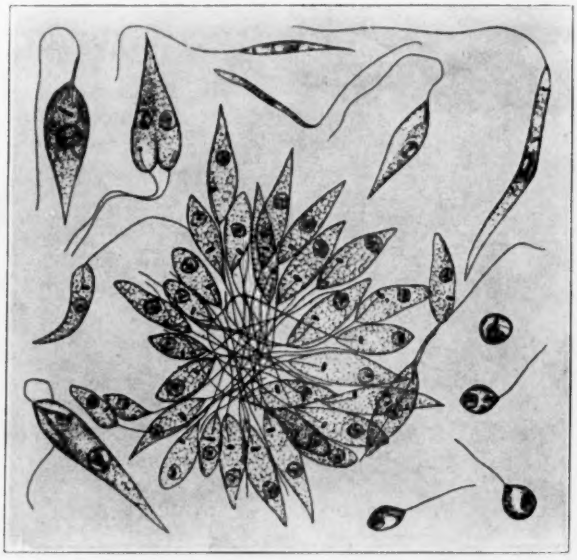

Fig. 4.—Culture forms of leishmania parasite, fixed with Schaudinn's fluid and stained with iron hematoxylin (× 2,000). (Photograph after Wenyon.[17])

groups. He inoculated rabbits with four strains of Leishmania (Donovani, infantum, tropica and braziliensis), and found that the serums of animals inoculated with Leishmania Donovani agglutinated this organism and also Leishmania infantum. This demonstrated the closer relationship of these two strains, which have been placed in one group. Leishmania tropica and Leishmania braziliensis, however, were agglutinated by their respective serums, and therefore retained their individual group identity.

17. Wenyon, C. M.: Protozoology, New York, William Wood & Company, 1926, vol. 2, p. 399.

18. Noguchi, H.: Proc. Internat. Conf. Health Problems of Trop. America, 1924, p. 455.

Clinically, the Leishman-Donovan bodies produce a group of diseases which is divided according to the cutaneous or visceral manifestations. The cutaneous forms are oriental sore (Leishmania tropica) and the generalized form (Leishmania braziliensis). The visceral forms are recognized as Indian kala-azar (Leishmania Donovani) and the Mediterranean or infantile form of kala-azar (Leishmania infantum). The discussion of the latter disease in children, with which we are concerned here, constitutes a chapter of no little interest and significance. We wish to emphasize that in choosing to deal with this condition as an entity, we are not unmindful of those who assert the identity of the two visceral forms of the disease.

History of Leishmania Infantum.—Jemma [19] and Laveran [20] presented a survey of the interesting historical landmarks in the recognition of Leishmania infantum. As early as 1835, Roeser [21] described a form of splenomegaly in children on the island of Spezia. In 1880, Cardarelli [21] noted the well known clinical picture long recognized under the name of *Pseudoleukemie or Anemia splenica infantilis oder infectiosa.* The disease was thereafter frequently referred to, but the etiologic agent was not discovered until Pianese,[22] in 1905, demonstrated parasites resembling the Leishman-Donovan bodies in the organs of several children ill with anemia splenica infantilis, and made the first pathologic examination of this condition. In 1904, Laveran and Cathoire [23] described the first case in an infant of 7 months, in Tunis. In 1908, Nicolle [24] and his co-workers named the parasite Leishmania infantum, and pointed out that in northern Africa the disease tended to be more common in infants than in adults. Nicolle was able to transmit the infection from man to monkeys and dogs and to demonstrate that the infection occurs spontaneously in dogs. It was he who suggested the hypothesis that the disease is carried from dog to man through an intermediate host. Thereafter the disease was recognized and described in Catania, Palermo, Rome and most of the Mediterranean area.

Since Noguchi's observations, the morphologic and serologic identity of the parasites causing the Mediterranean and the Indian form of kala-azar has been accepted. The opinion that the two forms are clinically identical is generally held. There are, however, numerous dif-

19. Jemma, R.: Ergebn. d. inn. Med. u. Kinderh. **23**:595, 1923.

20. Laveran, A.: Leismaniasis, Paris, Masson & Cie, 1917.

21. Quoted by Jemma.[19]

22. Pianese, R. I.: Gazz. internaz. med.-chir. **8**:265, 1905.

23. Laveran, A., and Cathoire, M.: Bull. Acad. de méd. Paris **51**:247, 1904.

24. Nicolle, C.: Arch. Inst. Pasteur de Tunis **1**:3 (Feb.) 1908; **2**:57 and 59 (April) 1908; **3**:104 and 109 (July) 1908; Compt. rend. Acad. d. Sc. **146**:498, 1908; Ann. Inst. Pasteur **23**:361, 1909.

ferences. These differences, essentially epidemiological, were strongly emphasized by Adler and Theodore [14] in their investigation of Mediterranean kala-azar.

Epidemiological Peculiarities.—Without attempting to give an epidemiological survey we shall note the important peculiarities. The infantile form of kala-azar lacks uniformity in distribution even in endemic regions. Altitude plays a rôle. In over 1,400 cases collected by Paradiso [25] in Sicily, none occurred above an altitude of 733 meters, the large majority occurring between sea level and 214 meters above. In Spain Pittaluga [26] found that no cases have been recorded above 650 meters. The disease is most commonly found among the poorer rural or semirural population. It is rare among the poorer urban population in large cities situated in endemic foci. The well nourished child of the wealthier classes usually escapes the disease even when residing in an endemic focus.

The period of incubation is not definitely known. It is given by Adler and Theodore as less than six months and, exceptionally, less than three months. This is somewhat longer than that given for the Indian form of the disease. Only 1 case has been reported in an infant of 1 month. The infantile form of the disease is rare, though not unknown in adults. The scarcity of organisms in the peripheral blood is another feature in striking contrast to the Indian form.

The peculiar relationship of the two forms of visceral leishmaniasis to the incidence of the infection in dogs is worth noting. It is remarkable that in India, where the adult form of kala-azar is widespread, dogs are rarely infected. In Greece and Italy, where the infantile form is endemic, leishmaniasis in dogs is widespread. It should be pointed out, too, that the relative incidence even of the infantile form of the disease in man and in dogs varies in different foci. In Palermo, one of the largest endemic centers, examinations of a large series of dogs by Jemma [27] and by Caronia and di Giorgio [28] showed that there was no infection present. In Catania, the largest of all endemic centers, Pulvirenti [29] found an infection rate of only about 1 per cent in dogs; on the other hand, in Athens, where the incidence in children is low, Cardamatis [30] found 13.8 per cent of the dogs infected.

These peculiar facts have aroused considerable interest and stimulated investigation. It is of further interest that though differences between the canine parasites and those of the human being have been

25 Paradiso, F.: Pediatria **24**:664, 1926.
26. Pittaluga, G.: Pamphlet Soc. d. Nat. Geneva, C. H. 368, 1925.
27. Jemma, R.; di Christina, G., and Cannata, S.: Pathologica **2**:250, 1910.
28. Caronia, G., and di Giorgio, G.: Pathologica **6**:208, 1914.
29. Pulvirenti, G.: Pathologica **3**:205, 1911.
30. Cardamatis, J. P.: Bull. Soc. path. exot. **5**:88, 1912.

observed, they are considered no greater than one might expect from varying strains of the human parasite. In this connection Wenyon [31] says, "It is safe to conclude that the parasites from man and the dog are identical."

Sporadic cases of the infantile form of kala-azar have been reported throughout the entire Mediterranean area. The disease is constantly present, however, in certain important foci. The three largest endemic centers are Catania, Palermo and Naples. Cases are also constantly observed in Tunis, Algeria, Spain, Malta, China, Greece and the southern part of Russia.

Transmission.—The occurrence of natural infection in the dog, the morphologic identity of the parasites causing the human and canine forms of the disease, the facts that the canine form may be produced by the human parasite, and that the canine parasite produces in other animals a picture identical with that induced by the human strain have given rise to the view that the dog is a reservoir for the virus. This point of view, however, is disputed, and it is claimed by many authors that the infection in the dog is as much an accident as is the infection in man. The question is not entirely settled. The most complete recent survey of this phase of the subject is that of Wenyon [31] in 1932. Experimentally, the mouse, the dog and the monkey can be infected. In recent years, since the work of Smyly and Young [32] and of Young, Smyly and Brown [33] in northern China, the hamster has been utilized as a more susceptible animal. The work of Adler and Theodore [14] and others with this animal has attracted attention.

The constant finding of organisms in the peripheral blood early gave rise to the idea that a blood-sucking insect was the carrier, and efforts of more recent years have been in this direction. Numerous attempts, however, to determine the intermediate host have been futile. Mosquitoes, lice, bedbugs, house-flies, fleas and dog-ticks have all been investigated, with unconvincing results.

Since the important observations of Knowles, Napier and Smith [34] in 1924 that the sand-fly Phlebotomus argentipes became heavily infected with parasites after feeding on patients with kala-azar, attention has been focused on the sand-fly as the intermediate host. Sinton [35] noted a correlation between the distribution of this species and the incidence

31. Wenyon, C. M.: Tr. Roy. Soc. Trop. Med. & Hyg. **25**:319, 1932.

32. Smyly, H. J., and Young, C. W.: Proc. Soc. Exper. Biol. & Med. **21**:354, 1923.

33. Young, C. W.; Smyly, H. J., and Brown, C.: Proc. Soc. Exper. Biol. & Med. **21**:357, 1923.

34. Knowles, R.; Napier, L. E., and Smith, R. V. A.: Indian M. Gaz. **59**:593, 1924.

35. Sinton, J. A.: Indian J. M. Research **11**:1035, 1924; **12**:701, 1925.

of Indian kala-azar—a correlation which was also observed in the species Phlebotomus perniciosus found in the Mediterranean area. Further studies by Adler and Theodore caused this insect to be considered a likely link. In his review of the entire subject Wenyon,[31] although pointing out that the evidence is strong that sand-flies are responsible for the spread of kala-azar and oriental sore, says that the problem has not yet been completely solved.

Incidence.—In his observations of more than 300 cases of the Mediterranean form of the disease between 1908 and 1923, Jemma [19] found that the condition manifested itself most commonly during the second and third years of life, the infection occurring most likely in the first and second years. Later Gabbi [36] pointed out that the greatest incidence is during the first five years. Statistics compiled by Paradiso in Catania for the period from 1915 to 1925 show the most striking age incidence in the first and second years of life. In Spain, Pittaluga made similar observations in a tabulation of 343 cases. It is reported that in Sicily 60 per cent of all of the cases occur in infants at the breast.

The literature contains numerous reports of the Mediterranean form of the disease in adults; most authors, however, agree that this form of kala-azar is essentially a child's disease. It has been suggested that Mediterranean adults are naturally immune to infection with Leishmania infantum.

Sex seems to play no rôle. The disease takes its toll in a poor environment, especially in the rural districts. Because of the nature and chronicity of the illness, attempts to describe a striking seasonal incidence have not been successful.

Clinical Course.—The onset is usually insidious. In the *initial stage,* fever, either high or low, intermittent or remittent, may be the only complaint. Chills are uncommon. Sweats accompany the fall in temperature and may be profuse and distressing. Gastro-intestinal symptoms are not uncommon. In some cases vomiting is profuse; in others there may be diarrhea with occasional bloody stools. Jemma observed epistaxis in a few cases. A distinct hemorrhagic tendency has been described in several instances. An increase in the size of the liver and spleen becomes noticeable.

In the *second* or *anemic* stage of the disease, the condition is well established. The child presents pallor of the skin and mucous membranes. The spleen is moderately enlarged, and the liver is similarly increased in size. Restlessness, loss of appetite, listlessness and irritability are common symptoms. Jemma described a marked somnolence in some cases. There is generally a loss of weight, which, however, need

36. Gabbi, U., quoted by Jemma.[19]

not be marked. The fever is persistent and, according to most observers, may be markedly irregular. The rise and fall of temperature constitute a unique feature of this disease. The double remission in twenty-four hours, best seen on a four-hour chart, may be diagnostic (fig. 2). It should be remarked, however, that during this stage the temperature may occasionally drop to normal for several days. These remissions may be of only short duration and are usually followed by periods of marked activity of the disease. Death from intercurrent respiratory infection during the anemic stage is not uncommon.

In most of the patients there is what is described as the *third stage* of the disease. By this time cachexia is apparent, and low, continued fever sets in, accompanied by severe anemia and emaciation. The liver and spleen become markedly enlarged. It has been pointed out that there is no constant relationship between the size of the spleen and the course of the disease. The spleen may be huge, occupying the left half of the abdomen, its lower pole presenting below the level of the umbilicus and its right margin extending over to the right border of the rectus muscle. The liver is usually not so markedly enlarged as the spleen, and may extend from 2 to 4 fingerbreaths below the costal margin. Occasionally, in terminal stages, the spleen has been noted to recede to the costal margin. In cases healing spontaneously or responding to specific therapy the shrinkage of the spleen may be striking.

In the later stages, edema of the extremities and a peculiar slate-gray pigmentation of the arms, legs and abdomen are not uncommon. There may be enlargement of the lymph glands and a peculiar dryness of the skin. The general cachexia and wasting of the patient make him susceptible to intercurrent infection, which may terminate the disease. Pneumonia, dysentery and cancrum oris are common terminal complications. Acute hemorrhages from the bowels, epistaxis, purpura, edema of the glottis and nephritis have been reported as additional complicating disorders.

Jemma [19] classified the disease according to chronicity. The acute form, which runs a rapid course of from thirty-five to forty days, is rare. The fever, anemia and swelling of the spleen are not remarkable in this form. The subacute form lasts for from about five months to one year. The majority of cases fall into this group. This is the type which, when not interrupted by intercurrent infection, runs the classic course ending in marked cachexia. The chronic form runs a slow course that may last two or more years. The disease may remain stationary for several months, or there may be a remission during which the spleen and the liver may recede and the anemia become markedly improved. These periods are followed by exacerbation which may end in death through cachexia or be terminated by intercurrent infection.

Pathology.—Shortt [37] and others pointed out that leishmaniasis is essentially a disease of endothelial tissue. In experimental production of the condition in monkeys, Shortt found that the endothelial cells are the chief carriers of the Leishman-Donovan bodies. Hindle and Thomson [38] described the pathologic changes caused by a Tunis strain of Leishmania infantum in Chinese hamsters. In general, it may be said that the changes that occur in the various organs are due to invasion of the endothelial cells of the capillaries and the macrophages and proliferation of these cells. The invaded cells are mostly concentrated in the spleen, bone marrow and liver, although the lymphatic glands or any organ may be found infected. The changes that occur vary in different cases. Jemma pointed out that whereas in the typical cases the parasites may be extensively distributed throughout all of the organs, in the less typical cases they may be limited to only a few organs.

The chief histologic changes in the organs are a marked increase in the number of macrophages, which are presumably derived from the reticulo-endothelial system or from the endothelial cells of the capillaries or from both. The free histiocytes and the reticulo-endothelial cells are infected with the Leishman-Donovan bodies. Parasites have occasionally been found in polymorphonuclear cells and in myelocytes. It has been suggested that the rupture of the distended endothelial cells liberates the parasites into the blood stream, whence they are carried by leukocytes to all viscera and redeposited in endothelial cells. Red cells apparently remain free from the organisms.

The greatly enlarged spleen shows an increase in fibrous tissue, with a multiplication of the macrophages, which are often loaded with parasites (fig. 5). In the later stages, the plasma cells, lymphocytes and infected macrophages of the splenic pulp enter the venous sinuses of the spleen. Similar changes occur in the liver, where the proliferation of free histiocytes and the accumulations of lymphocytes and plasma cells around the interlobular veins are prominent. The Kupffer cells may contain numerous parasites, and there is extensive proliferation of the endothelial cells. The fibrotic changes may be marked.

The bone marrow, which takes on the appearance of functioning lymph tissue, contains numerous infected cells. The lymph glands are enlarged and firm, and the tissue may be almost entirely replaced by the infected histiocytes and the reticulum cells.

Cloudy degeneration of the myocardium, the liver, kidney and other organs is a common finding. The subepithelial tissues of the wall of the intestine may be much swollen owing to the presence of an enormous number of macrophages. Rarely the meninges show evidence of inflam-

37. Shortt, H. E.: Indian J. M. Research **11**:186, 1923.

38. Hindle, E., and Thomson, J. G.: Proc. Roy. Soc. London, s.B **103**:252, 1928.

matory reaction. In a microscopic section, the endothelial cells of the capillaries contain numerous parasites.

In whatever part of the body the parasites are found, and they may occur in any organ or tissue, they are practically always within the cytoplasm of large cells of the endothelial type or the macrophages, and they always occur in the rounded nonflagellate stage.

Observations of the Blood.—The reaction of the blood to Leishmania infantum is important. Investigations have resulted in numerous confusing reports. A moderate anemia with leukopenia and relative lymphocytosis is most commonly reported. In the early stages, a normoblastic reaction and a myelocytic leukocytosis have been found.

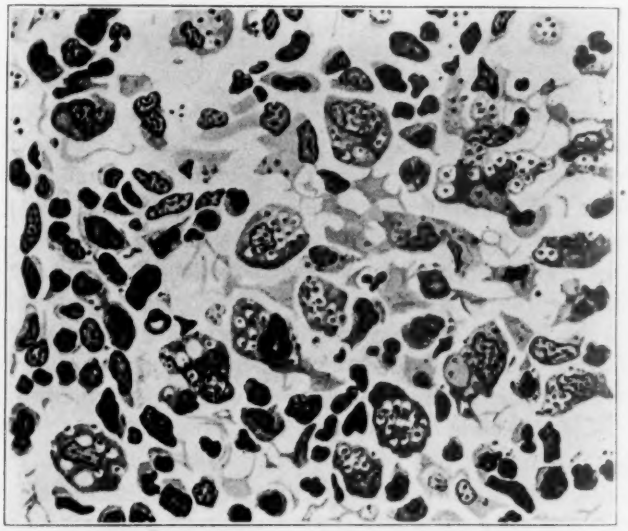

Fig. 5.—Section of the human spleen (× 750) showing leishmania parasites within the macrophages. (Photograph after Wenyon.[17])

In 22 cases Abate [39] found constant oligochromemia and oligocythemia. Frequent anisocytosis, occasional poikilocytosis and only occasional normoblasts were present. The leukocytes varied in number, showing marked leukopenia in some cases, less leukopenia in other cases and normal leukocytosis in still others. Occasionally leukocytosis occurred. Jemma [19] summarized the observations in the blood in his cases as follows:

> The red blood cells and hemoglobin are always diminished, in some cases more, in others less. The red blood cells are rarely normal. They are frequently markedly diminished; occasionally there is anisocytosis and poikilocytosis; rarely erythroblasts are present. Polychromatophilia is common. The color index is

39. Abate, A.: Malaria e mal. d. paese caldi **8**:68, 1917.

usually under 1. The white blood cells in the main show a leukopenia in 59 per cent of cases. Not seldom a normal or approximately normal white cell count may obtain (39 per cent of the cases). In some cases a mild leucocytosis may be found, with lymphocytes almost always predominating. The lymphocytosis is not marked, when one considers the age group. Eosinophilia is not uncommon; basophilia is rare.

The sedimentation time and the cholesterol findings in this disease, although presenting certain definite changes, are not pathognomonic. Napier and Henderson reported a markedly accelerated sedimentation time in 16 cases of proved kala-azar. Garcia, in an analysis of 27 cases of infantile kala-azar, found a constant and pronounced hypocholesteremia, ranging from 45 mg. to 108 mg. per hundred cubic centimeters. He also found a return to normal figures after treatment.

DIAGNOSIS

The diagnosis of the disease is suggested by the clinical course, blood findings and certain serologic tests. The diagnosis is finally established by the discovery of the parasite. This is usually accomplished by making cultures and films of material obtained by puncture of the liver, bone marrow or spleen. The latter operation, thoroughly described by Caronia,[40] is not entirely free from danger. In some cases, especially when the spleen was large and soft, the wound continued to bleed, and death resulted. The presence of ascites and the evidence of a hemorrhagic tendency are contraindications. Some observers hold that puncture of the liver is less dangerous. The results, however, are reported as less reliable. In our case, we chose rather to puncture the bone marrow.

In 1904, Christophers[41] showed that examination of ordinary blood films will sometimes reveal the parasite. Numerous films, however, may have to be examined before a parasite is found. When seen in the blood smears, the parasites are few and are enclosed in the macrophages and in cells of the polymorphonuclear variety. In Italy, Cannata,[42] after examining numerous films in each case, found parasites in 15 of 16 cases. The reports of examination of the peripheral blood smears in the Indian form of kala-azar have been more enthusiastic. Patton[43] showed the presence of Leishman-Donovan bodies in 100 per cent of 84 cases by examination of blood smears. In 50 per cent of his cases, Leishman-Donovan bodies were demonstrated in a single film.

40. Caronia, G.: Pediatria **30**:607, 1922.

41. Christophers, S. R.: Sc. Mem. Off. M. & San. Dept. Govt. India, n.s. 8, 1904.

42. Cannata, S.: Pediatria **22**:27, 1914.

43. Patton, W. S.: Indian J. M. Research **2**:492, 1914.

Donovan [44] reported the parasites in smears of blood from the finger in 93.2 per cent of cases in Madras. Knowles and Das Gupta [45] demonstrated parasites in 67 per cent of 70 cases by using thick films of peripheral blood.

Mayer and Werner [46] in 1914 and Wenyon [47] in the same year demonstrated the possibilities of culture of the organism in the peripheral blood. This possibility of diagnosis was verified by numerous Italian observers. In Peiping, Young and Van Sant [48] described a special method of inoculating a centrifugated specimen of blood in a modified N.N.N. culture medium by which they obtained positive results in 90 per cent. Adler and Theodore reported positive results in 91.7 per cent of 36 cases.

The blood is inoculated into a series of tubes of Locke blood agar or N.N.N. medium. The optimum temperature is usually given as from 22 to 27 C. Flagellates develop after a variable period usually given as from ten days to three weeks. A negative result does not exclude infection.

The serologic tests that are usually performed corroborate the diagnosis. The aldehyde (dilute formaldehyde-gel) test of Napier [49] is performed by the addition of 1 drop of 30 per cent formaldehyde to 1 cc. of clear, noninactivated serum from the patient. This is shaken and allowed to stand at room temperature. The result is considered as strongly positive when the serum "sets" in from one to three minutes and becomes opaque in from three to twenty minutes. In children the serum may not become so solid, and any degree of opacity is regarded as positive. From a study of 56 known cases of kala-azar Das Gupta [50] found that to get the most accurate results the test must be done as originally described. Chopra and Chaudhury [51] considered the time of gelation of the serum as of prognostic significance. If the time is over one-half hour, satisfactory progress may be assumed to be taking place. The test is not 100 per cent reliable. Cases are reported in which the Leishman-Donovan bodies have been found and the test has been negative. During the treatment of kala-azar with antimony the test becomes increasingly negative and eventually completely so.

The "globulin precipitation test" originally described by Brahmachari [52] in 1917 has been extensively used. This test has since been

44. Donovan, C.: Indian M. Gaz. **40**:411, 1905; Tr. Bombay M. Cong. 1909, p. 159.
45. Knowles, R., and Das Gupta, B. M.: Indian M. Gaz. **59**:438, 1924.
46. Mayer, M., and Werner, H.: Deutsche med. Wchnschr. **40**:67, 1914.
47. Wenyon, C. M.: J. Trop. Med. **17**:49, 1914.
48. Young, C. W., and Van Sant, H. M.: J. Exper. Med. **38**:233, 1923.
49. Napier, L. E.: Indian M. Gaz. **56**:238, 1921; J. M. Research **9**:830, 1922.
50. Das Gupta, C. R.: Indian M. Gaz. **66**:500, 1931.
51. Chopra, R. N., and Chaudhury, S. G.: Indian M. Gaz. **67**:265, 1932.
52. Brahmachari, U.: Indian M. Gaz. **52**:317 and 429, 1917.

modified, but in principle it most likely depends on the precipitation of excessive amounts of globulin from the blood serum by the addition of distilled water. In 1921, Ray [53] suggested the "hemolytic test" for kala-azar. In our case, the Sia modification [54] of the hemolytic test was used as suggested by Dr. Weech, who happened to see the case. The test is performed by the addition of 20 mm. of blood drawn into a hemoglobin pipet, to 0.6 cc. of distilled water in a test tube of from 7 to 8 mm. in diameter. This is mixed by whirling, and the tube allowed to stand. At the end of five minutes, a cloudiness indicates a positive test is performed by the addition of 20 mm. of blood, drawn into a hemoglobulin precipitation test in another form. Sia [56] showed that the intensity of the reaction can be evaluated from the rapidity of precipitation of the sediment. The test is reported as positive in schistosomiasis [57] and in certain severe anemias.

Attempts to obtain a satisfactory complement-fixation test have not been entirely successful. Similarly attempts to obtain a reliable cutaneous test have been unfruitful.

DIFFERENTIAL DIAGNOSIS

With the increasing knowledge of kala-azar—its etiology, clinical course, blood picture, serologic reactions and methods of discovering the parasite—the task of differentiating the disease from the numerous other conditions producing splenomegaly and fever has become relatively simple. In this country, where parasitic infestation and autochthonous splenomegaly of unknown etiology is less common, the problem is even less difficult. The condition must, however, be borne in mind, especially in dealing with immigrants from known endemic foci.

From bacterial infections such as typhoid the disease is readily distinguished. The rash, the characteristic alterations in the pulse, the tongue and the clinical course of typhoid suggest the diagnosis. Culture of the stool, blood and urine and the Widal reaction establish the diagnosis.

In undulant fever, the malaise, headache and pains in the joints are the prominent features. The agglutination reaction with Bacterium melitensis is of diagnostic importance.

It may often be difficult to differentiate the disease from malaria. The sharply defined paroxysms of the tertian and quartan variety and the generally severe symptoms of acute attacks may help. The finding

53. Ray, C.: Indian M. Gaz. **56**:9, 1921.

54. Sia, R. H. P.: China M. J. **35**:397, 1921.

55. Sia, R. H. P., and Wu, H.: China M. J. **35**:527, 1921.

56. Sia, R. H. P.: China M. J. **38**:35, 1924.

57. Faust, E. C., and Meleney, H. E.: Am. J. Hyg. (monog. ser. no. 3) March 1924, p. 229.

of the parasite in the blood makes the diagnosis certain. It is the chronic form of malaria, however, that often presents difficulty. The patient may look and feel relatively well and the blood reveal no parasites. The quinine test may be diagnostic. When kala-azar is strongly suspected, however, puncture of the spleen or bone marrow and culture may be necessary to establish the diagnosis.

Other protozoan infections may need to be excluded. In trypanosomiasis, the frequent neurologic signs and the finding of the parasites in the blood are distinguishing features. Kala-azar may be distinguished from ancylostomiasis, by the failure to find parasites in the stool and the positive evidence obtained on visceral puncture.

Specific abscess of the liver due to the ameba is distinguished by the history, the localizing signs and the results of visceral puncture.

The so-called Egyptian splenomegaly most likely falls into the group of helminthic infestations. These conditions are a common cause of anemia, fever and splenomegaly in Asia, Asia Minor and on the European continent. The procedures usually employed in such conditions will help establish the diagnosis. Final differentiation may be achieved by puncture of the spleen or the bone marrow.

In the Gaucher group, pingueculae, the familial incidence, the changes in the bones, the absence of a low red cell count and the absence of atypical fever curve suggest the diagnosis. Whenever any difficulty presents itself, a study of the juice of the spleen or bone marrow will be diagnostic.

So-called Banti's disease progresses through definite stages. The anemia is more marked. Hemorrhages are more common. Jaundice and ascites are fairly common late in the disease. Rogers [58] observed that Banti's disease has been mainly met with in areas in which infantile kala-azar exists, and that at least one museum specimen removed for Banti's disease showed abundant organisms of kala-azar. In view of the etiologic obscurity of Banti's disease and the fact that many cases so diagnosed have been demonstrated to be other pathologic entities, the right to make this diagnosis has recently been questioned. It has been suggested that in cases of so-called Banti's disease it might be well to investigate smears from the spleen for Leishman-Donovan bodies.

The differentiation of infantile kala-azar from thrombosis of the splenic vein and primary cirrhosis of the liver presents little difficulty. In the former, the course, the leukopenia and a history of hematemesis with shrinkage of the spleen help make the diagnosis. When the thrombosis spreads to the portal system, ascites may be observed.

Primary cirrhosis of the liver is rare in childhood. The shrinkage of the liver, hematemesis and the development of ascites and of a visible collateral circulation are suggestive signs.

58. Rogers, L.: Fevers of the Tropics, ed. 3, New York, Oxford University Press, 1919, p. 1.

There are many other conditions in childhood which are characterized by anemia and splenic enlargement, such as chronic infections, metabolic disturbances, nutritional disturbances, syphilis, tuberculosis and rickets. The clinical picture and the serologic and therapeutic tests are usually sufficient to establish the diagnosis in these. Failing this, resort may be had to puncture of the bone marrow or visceral puncture, although this will rarely, if ever, be necessary.

There are numerous dyscrasias of the blood presenting hepatosplenomegaly and fever in which intensive study of the blood will establish the diagnosis. Some of these, notably hemolytic icterus and sickle cell anemia, are familial. In the former, studies of the bile pigment of the blood and the fragility test are of diagnostic importance. Evidence of marked stimulation of the bone marrow is a striking feature. Sickle cell anemia presents a racial incidence and alterations in the red corpuscles which are diagnostic.

True hemorrhagic thrombocytopenic purpura presents a characteristic diminution in the platelet count and a clinical picture that is strongly suggestive. The prolonged bleeding time and delayed retraction of the clot are important.

Diseases of the blood such as leukemia may be excluded by the absence of a typical blood picture. In pernicious anemia, rarely found in childhood, wasting is unusual, and hepatomegaly and splenomegaly are not marked. The blood picture and the therapeutic response to liver are of diagnostic value.

In the lymphogranuloma group, the clinical course and biopsy of a lymph gland will usually establish the diagnosis. Puncture of the spleen or bone marrow will rarely have to be resorted to in order to rule out leishmaniasis.

The large group of anemias with splenomegaly in childhood which since 1889 went under the name of von Jaksch's disease [59] is rapidly disappearing as a clinical entity. It is from this group that Cooley [60] and his co-workers in 1925 extracted the symptom complex which they subsequently called the erythroblastic anemia of childhood. The early observation that this disease is limited to children of the Mediterranean group of races has not yet been disproved. This fact makes the differentiation from infantile kala-azar particularly important. Morphologic study of the blood and roentgenologic study of the bones will aid in the diagnosis. Microscopic observations on the organs, especially the liver, spleen and bone marrow, are unlike those of kala-azar.

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59. von Jaksch, R.: Wien. klin. Wchnschr. **2**:435, 1889; Prag. med. Wchnschr. **15**:387, 1890.

60. Cooley, T. B., and Lee, P.: Tr. Am. Pediat. Soc. **37**:29, 1925; Cooley, T. B.; Witwer, E. R.; and Lee, P.: Am. J. Dis. Child. **34**:347 (Sept.) 1927.

The etiology of erythroblastic anemia is still obscure. It should be noted in passing that the possibility of an infection with leishmania as the basis for this disease was considered early. A spleen from a splenectomized patient was searched for parasites by Dr. F. G. Novy.[61] In other pathologic reports, the search for parasites is only rarely mentioned; very likely, however, a search was made without success.

In our discussion of differential diagnosis we have not attempted to detail all of the characteristic differences of the condition mentioned or to enumerate all the causes of splenomegaly and anemia in childhood. These constitute a confusing chapter, which should be the subject for special consideration elsewhere. The intention has been rather to emphasize the usefulness of puncture of the viscera and bone marrow and culture in cases in which kala-azar is strongly suspected, and the usual laboratory and clinical findings have failed to establish the diagnosis.

TREATMENT

The treatment of kala-azar is important because it is specific. Working in Brazil, Vianna[62] tried intravenous injections of antimony tartrate for a mucocutaneous leishmania disease known as espundia. His success encouraged di Cristina and Caronia[63] in Sicily to introduce this treatment for visceral leishmaniasis in children. They published a report on their first series of 8 cases in 1915. Five of the patients were cured, 2 were greatly improved, and only 1 died of nephritis. The use of the drug was thereafter rapidly accepted in India[58] and elsewhere. Its effectiveness in treating visceral and cutaneous kala-azar was readily demonstrated.

The literature reporting the success of the drug is now profuse. Some of the most critical analyses of its therapeutic value emanate from India and China, as well as from the Mediterranean area.

Numerous modifications of the original drug and methods of administration have appeared. The dose of antimony and potassium tartrate or its corresponding sodium salt usually given to children is small to start with: 0.015 Gm (¼ grain), or even 0.0075 Gm. (⅛ grain) or less. This is gradually increased by 0.0075 Gm. (⅛ grain) or 0.015 Gm. (¼ grain) until about 0.10 Gm. (1½ grain) is reached in the average child. A 1 per cent solution is used, and injections are given every third, fourth or fifth day. Some advise giving the drug even more frequently. A total dosage of about 1.6 Gm. or 2.0 Gm. (from 25 to 30 grains) is considered adequate for the average child.[64]

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61. Novy, F. G., quoted by Cooley, T. B.: Am. J. Dis. Child. **33**:786 (May) 1927.

62. Vianna, G.: Arch. brazil. de med. **2**:426, 1913.

63. di Cristina, G., and Caronia, G.: Bull. Soc. path. exot. **8**:63, 1915; Pathologica **7**:82, 1915.

64. Personal communication from Dr. Francis O'Connor to author.

Injections should be freshly prepared and given cautiously. Freshly distilled water, a saline solution or a 5 per cent solution of dextrose may be used as the diluent. Escape of the solution into the surrounding tissues during administration may be followed by severe inflammatory reactions and often necrosis. Nephritis, diarrhea, heart disease and pulmonary tuberculosis are considered contraindications to treatment.

The dosage must be kept within the limits of tolerance of the patient and must not be increased too rapidly. Coughing, a sense of constriction of the throat, dyspnea, nausea and vomiting are toxic symptoms and are indications for decreasing the succeeding dose. A temperature rise following administration of the drug, when not too severe, need not give cause for alarm. The urine must be examined frequently during the course of treatment for evidence of renal irritation.

In studying the effectiveness of antimony and potassium tartrate in the treatment of kala-azar in children of North China, Scott and Li [65] gave intravenous injections of the drug every third day, using either a 1 or a 2 per cent solution. They started with 0.5 cc. and rarely gave more than 4 cc. of a 1 per cent solution. Their total average dose was 0.87 Gm. administered in an average of thirty-seven injections. The average stay in the hospital was one hundred and four days. They pointed out, however, certain disadvantages in the use of this drug. Reactions to this preparation were more frequent; a longer time was required to complete the course, in comparison with other antimony preparations, and there seemed to be a direct relation between the use of the drug and the frequent occurrence of bronchopneumonia during the course of treatment.

An attempt to find an antimony compound which would give the maximum therapeutic effect with the least toxic manifestations led Napier,[66] Brahmachari,[67] and others to study numerous pentavalent antimony compounds which have since practically replaced antimony tartrate. These are a combination of urea with *para*-amino-phenyl stibinic acid, *meta*-chlor-*para*-acetyl-amino-phenyl stibinate of sodium, nitrogen glucoside of sodium *para*-amino-phenyl stibinate, amine salt of *para*-amino-phenyl stibinic acid, sodium salt of *para*-amino-phenyl stibinic acid and acetyl-*para*-amino-phenyl stibinate of sodium, which are now available under various trade names. Their action is reported

65. Scott, A. V., and Li, P. K.: Arch. Dis. Childhood **7**:213, 1932.

66. Napier, L. E.: Indian J. M. Research **19**:705, 1932; Pentavalent Compounds of Antimony in the Treatment of Kala Azar, Indian J. M. Research **14**:263, 1926; **15**:181, 1927; **16**:141, 901 and 911, 1928.

67. Brahmachari, P., and Brahmachari, U. N.: J. Trop. Med. **34**:263, 1931. Brahmachari, U. N., and Maity, B. B.: Chemotherapy of Antimony Compounds: Period at Which Sterilization of Peripheral Blood Takes Place During Treatment with Urea Stibamine, Indian J. M. Research **13**:21, 1925.

as quicker and less toxic. They have the further advantage in children of being suitable for intramuscular injection and are marketed in sealed ampules ready for dissolving in sterile water. It is claimed by some investigators that several of these compounds are liable to toxic decomposition.

Para-amino-phenyl-stibinic acid and urea stibamine are the two especially recommended. The former is considered one of the most effective as well as one of the least toxic of the antimony preparations. An intensive course of treatment with this drug, in which injections were given daily, was successfully used by Napier and Mullick.[68] They reported a death rate of only 2 per cent in the treatment of 175 unselected adults and children with kala-azar. Eight injections were given at daily intervals. Children under 50 pounds (22,679.60 Gm.) received an initial dose of 0.1 Gm. or less; this was increased by the second or third injection to 0.2 Gm., and this dose continued for the remainder of the treatment.

Scott and Li similarly found that the amine salt of *para*-amino-phenyl-stibinic acid required the shortest period of administration for the full course and provoked relatively little reaction. Furthermore, the drug could be given intramuscularly with equal effectiveness. The initial dose used was 0.05 Gm., which was increased to 0.1 Gm. for the second injection and then to 0.2 Gm. for the remainder of the course. Children in fairly good condition or with noma were given daily injections. The average total dose for 34 patients so treated was 1.6 Gm. The average stay in the hospital was thirty days, and the average number of injections, eleven.

Whatever drug is chosen for the specific treatment, the usual adjuvants such as high caloric diet rich in vitamins and rest in bed should be insured, if results are to be obtained early.

The signs indicative of improvement under treatment appear in the following order:[65] (*a*) cessation of fever, (*b*) increase in body weight, (*c*) reduction in the size of the spleen and liver, (*d*) increase in the total leukocyte count, (*e*) increase in hemoglobin and in the red cell count and (*f*) improvement in physical appearance and well-being.

It is important to remember that though improvement may take place rapidly, the parasites may persist in the spleen and be culturable even up to two months after the commencement of treatment. Experience has shown that negative results from puncture and culture of the spleen, though significant, are not proof that Leishmania is absent from the body. The characteristic changes in the serum globulin may remain in cured patients for several months following completion of the treatment. Scott and others suggested that if clinical improvement continues for two months after the course of antimony is finished, the patient

68. Napier, L. E., and Mullick, M. N.: Indian M. Gaz. **63**:445, 1928.

is cured. Napier pointed out that relapses may occur within a period of six months after apparent cure, although their occurrence after the first three months is rare. It seems necessary, therefore, that patients apparently cured be examined for a period of at least three months after treatment is stopped to make certain that there is no recurrence.

PROGNOSIS

The prognosis in cases of kala-azar is good if treatment is begun early and pursued thoroughly. A continuous course is necessary for success. Broken treatment leads to the organism's becoming "antimony-fast." Failure of progress under treatment, as shown by the cessation of shrinkage of the spleen, should be combated by change of the drug to one of the other compounds mentioned. It must, however, be remembered that recovery continues after the treatment is completed.

The rarity of reinfection has been taken to mean that in the majority of cases some immunity is established by the disease.

Without treatment, the disease commonly ends fatally, although a percentage of recoveries may occur spontaneously. Jemma estimates the percentage as from 14 to 16. Recovery has also been noted after certain bacterial infections, which seem to act adversely on the parasites. The duration of untreated cases may be only a few months in the acute forms of the disease, or several years in the more chronic types.

The progress made in successfully combating this disease can be realized from the following statement made by Napier and Mullick in 1928, "Thirteen years ago, the death rate in Kala Azar was said to be 95 per cent . . . whereas now, at whatever stage of the disease the patient first comes under treatment, the recovery rate should be at least 95 per cent."

SUMMARY

1. A case of infantile kala-azar in a Greek child is presented, and his progress under treatment is reported. This is the fourth case of the disease reported in the American literature.

2. A clinical and pathologic survey of infantile kala-azar, with a review of the three cases previously reported in the United States, is given.

3. The epidemiology of the disease is briefly discussed.

4. The ease of diagnosis by puncture of the bone marrow is stressed, and the usefulness of this procedure is urged in investigations of diseases of the hemopoietic system and in splenomegalies of undetermined origin. This is a simpler and safer procedure than puncture of the spleen.

5. Specific therapy is outlined, and the need for uninterrupted treatment is emphasized.

2 East Ninety-Fourth Street.

Pediatric Biographies

ANDREAS RITTER VON HÜTTENBRENNER
1842-1905

A NOTE ON THE HISTORY OF PYELITIS

JOHN RUHRÄH, M.D.
BALTIMORE

Andreas Ritter von Hüttenbrenner was born on Jan. 2, 1842, in the old university town of Graz, but he went to Vienna to study and was graduated there in 1865. He then served as an assistant to Wiederhofer in the University Children's Clinic and in 1875 was qualified to lecture on pediatrics. In 1879 he took charge of the Karolinen-Kinderspital. He wrote chiefly on pediatrics and pathologic anatomy, and his volume on the diseases of children, "Lehrbuch der Kinderheilkunde," which appeared in Vienna in 1876, is full of sound sense and careful observations. A second edition was issued in 1888. Von Hüttenbrenner contributed many articles to the *Zeitschrift für Heilkunde* and was one of its staff. Little is recorded concerning his life in the sources accessible to me. He died in May 1905.

His chief and perhaps only claim to recognition in pediatric history is the fact that he was one of the first, if not actually the first, to describe pyelitis. This he did in the first edition of his book. If there is an earlier account of this condition, I have failed to find it.

His definition of the disease is as follows:[1]

> Pyelitis.—The inflammation of the calyx and pelvis of the kidney is a very common disease in childhood and may easily be overlooked or mistaken for and treated as some other condition. Moreover, it often happens that it is found accidentally at autopsy in an illness which appears to have no relationship to it, for instance, in infants with intestinal catarrh, enteritis, and so forth. The mucous membrane of the calyx and pelvis is found moderately injected and dilated and filled with a cloudy, purulent urine. Upon investigation of such urine, besides the pus cells, a great amount of detached cylindrical epithelium and ammonium, urates, or phosphates of ammonium magnesia are found. It appears that the thickened urine in many intestinal diseases acts as an irritant on the mucous membrane and becomes the cause of the catarrhal condition.
>
> If the pyelitis appears as a separate disease, vague signs precede, such prodromes as are noted in many acute diseases. It may start with vomiting so that one might think some other febrile disease was beginning.

1. von Hüttenbrenner, A. R.: Lehrbuch der Kinderheilkunde, Vienna, Wilhelm Braumüller, 1876.

Children run a moderate fever continuously, the fever shows no noteworthy typical exacerbation, the pulse is accelerated, the appetite is poor, tongue coated, and there is a bad odor from the mouth. The urine is cloudy, not diminished in quantity, the specific gravity is not noticeably lower, the reaction is slightly acid or neutral, albumin is present in small amounts. The microscopic examination shows, in addition to the crystals of sodium urate, pus corpuscles in moderate number, isolated red blood corpuscles, numerous epithelial cells from the calyx and pelvis, and so forth. No renal epithelium or hyaline casts are found in case the parenchyma is unaffected.

If the inflammation is merely confined to the pelvis, then micturition is almost without pain, but often the illness is associated with an acute cystitis, so that frequent spasms of the bladder occur which may be very painful. One recognizes a complicating cystitis by the quantity of pus and the detached bladder epithelium. Such urine sediments easily and often one-half of it is pus. Very rarely does a parenchymatous infection develop from such an affection of the kidney. This might manifest itself through familiar signs in the urine and in early edema which is always lacking in pyelitis. Only in rare cases is there painfulness to touch in the lumbar region, or do the children complain of a dull pain in the renal region. Still not much reliance can be put upon this symptom, as older children often have pains of a rheumatic nature or after gymnastics.

The course of a pyelitis is generally favorable, no further secondary diseases arise. The duration is from eight days to three or four weeks, during which time the children should be kept in bed as long as they have a fever. Later moderate exercise in the open air may be allowed. The food should be easily digestible, as soup, milk, and fresh vegetables. Meat should be avoided for a few days. When the quantity of pus first decreases, some rare meats might be ordered. One should avoid all sharp diuretics as they only irritate the kidneys. For dilution of the urine, various mineral waters (Preblaner, Giesshübler or Emser Kränchen) in large quantities may be prescribed and during the time little of the ordinary drinking water should be taken. Children, who have once had pyelitis, are susceptible to recurrences.

Pediatrics in Art

ANIMALS AS WETNURSES

JOHN RUHRÄH, M.D.
BALTIMORE

Animals to replace the mother's breast occupy a considerable place in art and literature. Perhaps the best known example is that of the bronze antique now in the Capitol Museum in Rome. It figures Romulus and Remus nursing at the dugs of a wolf. The succession of the kings

Bronze antique showing Romulus and Remus nursing at the dugs of a wolf.

of Alba, descendants of Aeneas, passed from father to son and finally came to two brothers, Numitor and Amilius. The younger brother, Amilius, obtained the throne and killed his brother's son, Lausus, while out hunting in order to secure the succession to his own son. He forced Rhea Silvia, the sister of Lausus, to become a vestal virgin. Falling asleep near a fountain she was seen by Mars, who fell in love with her. Her sons, Romulus and Remus, were seized by Amilius and put in a cradle and launched on the Tiber, which was at flood height. When the water receded the twins were deposited at the foot of the Palatine, where they were suckled by the wolf and then cared for by a shepherd and his wife. This is a classic example of the use of wolf's milk in infant feeding.

News and Comment

GENERAL

Physicians Certified by American Board of Pediatrics

The following applicants have been certified by the American Board of Pediatrics:

A. F. Abt, Chicago; D. P. Arnold, Buffalo; M. H. Bass, New York; B. I. Beverly, Chicago; R. A. Black, Chicago; J. R. Boulware Jr., Lakeland, Fla.; E. Boyd, Minneapolis; C. E. Bradley, Tulsa, Okla.; A. Capper, Philadelphia; P. C. Carson, Wichita, Kan.; S. Cohn, San Francisco; G. L. Cook, Tampa, Fla.; E. P. Copeland, Washington, D. C.; A. M. Dannenberg, Philadelphia; B. S. Dunham, Toledo, Ohio; P. W. Emerson, Boston; O. A. Faust, Albany, N. Y.; H. M. Gilkey, Kansas City, Mo.; J. H. Green, Waterbury, Conn.; C. G. Grulee, Evanston, Ill.; B. Haessler, Milwaukee; W. M. Happ, Los Angeles; G. Heller, Englewood, N. J.; J. H. Hess, Chicago; C. L. Holland, Fairmount, W. Va.; C. H. Hoover, Lancaster, Pa.; G. P. Hunt, Pittsfield, Mass.; M. Ingall, Boston; G. L. Johnson Jr., Englewood, N. J.; J. A. Jones, Philadelphia; F. H. Lamb, Los Angeles; E. Lewis, Washington, D. C.; C. S. Lipsitt, New Bedford, Mass.; W. London, Perth Amboy, N. J.; W. D. Lyon, Akron, Ohio; S. D. Mills, Westfield, N. J.; A. G. Mitchell, Cincinnati; F. T. Mitchell, Memphis, Tenn.; H. J. Morrison, Savannah, Ga.; H. T. Nesbit, Dallas, Texas; S. Newman, Danville, Va.; M. M. Nicholson, Washington, D. C.; I. Okin, Passaic, N. J.; C. C. Payne, Dayton, Ohio; H. H. Perlman, Philadelphia; J. J. Pollack, Detroit; N. A. Pokorny, Springfield, Mass.; R. E. Pray, Fargo, N. D.; J. A. Ritter, Philadelphia; J. H. Root, Waterbury, Conn.; E. Rosamond, Memphis, Tenn.; H. A. Rosenbaum, Chicago; L. C. Rosenberg, Newark, N. J.; O. W. Rowe, Duluth, Minn.; H. F. Rowley, Rochester, N. Y.; H. Sherwin, Brooklyn; F. B. Smith, Baltimore; L. H. Smith, Portland, Ore.; R. W. Stahr, Fort Dodge, Iowa; M. Winters, Indianapolis; D. Worthington, White Plains, N. Y.

Examinations by American Board of Pediatrics.—The American Board of Pediatrics reports the following results of examinations held in 1934:

	Total Number Examined	Passed	Failed	Percentage of Failures
Group 1.....	10	7	3	30
Group 2.....	19	15	4	21
Group 3.....	24	17	7	29
Total	53	39	14	26.4

UNIVERSITY NEWS

The University of Vienna will give its usual postgraduate course from Feb. 11 to Feb. 24, 1935.

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

EXPERIMENTS ON THE GROWTH AND LONGEVITY OF THE WHITE MOUSE. 1. THE INFLUENCE OF INJECTIONS OF THORIUM OLEATE IN OLEIC ACID, AND OF OLEIC ACID ALONE, ON GROWTH AND LONGEVITY. T. B. ROBERTSON, M. C. DAWBARN, R. G. THOMAS, J. W. WALTERS and J. D. O. WILSON, Australian J. Exper. Biol. & M. Sc. **11**:99 (June) 1933.

The growth of the animals which received subcutaneous injections of an emulsion of 1 per cent thorium oleate in oleic acid at short intervals (from one to two weeks) up to four hundred days was below that of the controls. The dose consisted of 0.25 cc. for animals under, and 0.5 cc. for animals over, 20 Gm. in weight of a solution containing 0.0018 Gm. of thorium dioxide per cubic centimeter. Growth was not influenced by injections of oleic acid alone. Duration of life was shortened by injections of both oleic acid and thorium oleate. In animals receiving thorium some of the metal was retained, the amount recovered after death being from 16 to 60 per cent of that injected and being present principally in the bones, skin and kidneys.

GONCE, Madison, Wis.

EXPERIMENTS ON THE GROWTH AND LONGEVITY OF THE WHITE MOUSE. 2. THE INFLUENCE OF THE CONTINUOUS ADMINISTRATION OF VEGETABLE NUCLEIC ACID AND THE INTERMITTENT ADMINISTRATION OF THYROID UPON GROWTH AND LONGEVITY. T. B. ROBERTSON, M. C. DAWBARN, J. W. WALTERS and J. D. O. WILSON, Australian J. Exper. Biol. & M. Sc. **11**:219 (Sept.) 1933.

The growth of mice which received 25 mg. daily of vegetable nucleic acid and small amounts of thyroid preparation (from 1.5 to 3 mg.) for one, two or three twenty-eight day periods was reduced below that of the controls. The duration of life was increased when thyroid extract was fed for only one period (from the sixth to the tenth week). The latter effect was negatived by a second period of administration of thyroid preparation and reversed by a third, so that the duration of life was diminished.

GONCE, Madison, Wis.

A STUDY OF THE EFFECTS OF AGAVE CONCENTRATE IN THE TREATMENT OF EXPERIMENTAL NEPHRITIS INDUCED IN ANIMALS. I. NEPHRITIS INDUCED IN RABBITS BY THE USE OF TARTRATES. II. NEPHRITIS INDUCED IN DOGS BY THE USE OF URANIUM NITRATE. HERMAN D. JONES, J. Pharmacol. & Exper. Therap. **48**:1 (May) 1933.

1. Among the natives of Central Mexico, the juice of the maguey plant (Manso fino, Agave atrovirens, Karw) has for generations been credited with having valuable therapeutic properties, particularly relating to kidney dysfunction. Tartrates damage the kidneys of rabbits (chiefly the epithelium), leading to retention of nonprotein and urea nitrogen and creatinine. The use of agave concentrate (fresh unfermented aguamiel juice concentrated under 20 mm. vacuum at from 35 to 38 C. [95 to 100.2 F.] to a density of from 38 to 39° Baume) lessened the retention of these substances, lowered the mortality considerably and decreased the renal damage.

2. In a similar manner, agave concentrate decreased the toxicity of uranium for dogs (uranium causes glomerular and tubular damage), but less strikingly than it did that of the tartrates for rabbits.

PILCHER, Cleveland.

QUANTITATIVE DETERMINATION OF PHOSPHATIDES IN THE BLOOD. H. FESTEN, Nederl. tijdschr. v. geneesk. **77**:1118 (March 11) 1933.

A method is described for the quantitative determination of phospholipoids in 0.2 cc. of blood. In order to get the phosphatides from the blood in a pure solution, Festen follows the method indicated by Bloor; after destruction he determines the quantity of phosphoric acid after the method of Tisdall.

VAN CREVELD, Amsterdam, the Netherlands.

DETERMINATION OF THE FAT CONTENT IN A SMALL QUANTITY OF BLOOD. H. FESTEN, Nederl. tijdschr. v. geneesk. **77**:1893 (April 29) 1933.

A method for the determination of the quantity of fat (fatty acids) in 0.2 cc. of blood is described. This is based on the following principle: The fat is saponified, and the amount of fatty acids is titrated. The alcohol-ether extract of the blood is purified by extraction with purified petroleum benzine. The extract contains no dextrose, and the formation of organic acids from the sugar by the sodium hydroxide used for the saponification of the fats is therefore excluded. A buret used for the titration of the small quantities of the fatty acids is described.

VAN CREVELD, Amsterdam, the Netherlands.

PARTS OF HUMAN LEUKOCYTES WHICH CAN BE COLORED BY SUDAN. J. H. C. RUYTER, Nederl. tijdschr. v. geneesk. **77**:2026 (May 6) 1933.

Human leukocytes were studied in slides with regard to the number of lipoid granules which can be colored by sudan. It appeared that with different methods of fixation the number of lipoid granules varied greatly.

VAN CREVELD, Amsterdam, the Netherlands.

Nutrition

STUDIES IN THE PHYSIOLOGY OF VITAMINS. XXII. EFFECT OF EXPERIMENTALLY INDUCED HYPERTHYROIDISM ON THE VITAMIN B REQUIREMENT OF PIGEONS. GEORGE R. COWGILL and M. L. PALMIERI, Am. J. Physiol. **103**:146 (July) 1933.

Pigeons with experimentally induced hyperthyroidism required a greater maintenance dose of vitamin B than "normal" controls, indicating a relationship between the amount of vitamin B required for maintenance of the body weight and the metabolism of the organism.

NOURSE, Cleveland.

A STUDY OF VITAMIN A DEFICIENCY IN NORMAL AND DEPANCREATIZED DOGS. ELAINE P. RALLI, ARTHUR PARIANTE, GERALD FLAUM and ALICE WATERHOUSE, Am. J. Physiol. **103**:458 (Feb.) 1933.

Depancreatized dogs showed symptoms of vitamin A deficiency that were not corrected by feeding or by injecting vitamin A in a potent form. It is suggested that the failure to utilize vitamin A may be related to the disturbance of the fat metabolism.

NOURSE, Cleveland.

THE TIME AT WHICH CASEIN BEGINS TO BE FORMED IN THE BREAST DURING PREGNANCY. ORAN I. CUTLER and JULIAN H. LEWIS, Am. J. Physiol. **103**:643 (March) 1933.

In cows, casein was found in the udders after the middle of pregnancy, between the twentieth and the twenty-fifth week. The blood of lactating animals did not show the presence of casein with the tests used.

NOURSE, Cleveland.

ROENTGENOGRAPHIC VISUALIZATION OF SUBPERIOSTEAL HEMORRHAGE IN INFANTILE SCURVY. W. E. NELSON, W. M. DOUGHTY and A. G. MITCHELL, J. A. M. A. **101**:14 (July 1) 1933.

Subperiosteal hemorrhages in infantile scurvy may not be visualized roentgenographically until calcium salts have been deposited following the administration of vitamin C. Demonstration of calcium in the periosteum surrounding the hemorrhage indicates healing. Unless serial roentgenograms are taken after the administration of vitamin C the diagnostic subperiosteal hemorrhage may be overlooked.

BONAR, Salt Lake City.

SIGNIFICANCE OF THE WATER METABOLISM IN HEALTH AND DISEASE. IRVINE MCQUARRIE, J. Pediat. **3**:539 (Oct.) 1933.

A review of the field of water metabolism in relation to clinical medicine is presented. The subject is discussed under the following headings: the chemical nature of water; the content and distribution in the body; essential items in water balance; the water requirements of the body; the regulation of water content and exchanges; the interchange of water through living membranes; the effects of various ions; the influence of diet; the rôle of phospholipids and cholesterol; the endocrine and nervous factors; the state of hydration and resistance to infections, and the water content and functional activity of nerve tissue.

LEMASTER, Evanston, Ill.

THE SERUM ALBUMIN AND GLOBULIN OF NEWBORN, PREMATURE AND NORMAL INFANTS. DANIEL C. DARROW and M. KATHARINE CARY, J. Pediat. **3**:573 (Oct.) 1933.

The serum concentration of total protein, albumin and globulin was determined in twenty new-born infants, twenty-six premature infants, fourteen normal infants about 5 months old and twenty-five infants suffering from various diseases. The data form a standard for evaluating the protein concentration during the first year of life. The total protein was decreased in all the infants, chiefly owing to low globulin, which was most evident in the premature infants. Infectious processes caused an increase in globulin in some of the infants. The authors suggest that the low globulin in infants may indicate a lack of the stimuli that give rise to the production of globulin in adults.

LEMASTER, Evanston, Ill.

DETERMINING APPROPRIATE WEIGHT FOR BODY BUILD. HELEN BRENTON PRYOR and HERBERT R. STOLZ, J. Pediat. **3**:608 (Oct.) 1933.

The width-length index of body build was determined on 4,560 school children. By this method, a more accurate objective figure representing the nutritional status is obtained than by using the Baldwin-Wood tables of average height and weight at various ages. In obtaining this index the bi-iliac diameter is divided by the standing height and multiplied by 100. The advantages of using the distance between the iliac crests as the criterion of body width are discussed. Comprehensive tables summarizing the results of the measurements are included.

LEMASTER, Evanston, Ill.

VITAMIN A DEFICIENCY IN INFANTS. KENNETH D. BLACKFAN and S. BURT WOLBACH, J. Pediat. **3**:679 (Nov.) 1933.

The authors report on thirteen infants in whom lesions characteristic of vitamin A deficiency were found at necropsy. A brief summary of the present knowledge referable to vitamin A deficiency is presented. In six of the patients a clinical diagnosis was made during life because of keratomalacia. In the remaining

seven patients the diagnosis was made by finding stratified keratinizing epithelium at necropsy. The following points are of value in detecting early signs of vitamin A deficiency: (1) dietary history; (2) a history of morbid processes interfering with the absorption of fat; (3) night blindness and xerosis of the cornea, and (4) demonstration of keratinized epithelial cells in scrapings from the cornea, nose, mouth and secretions of the trachea, kidneys and vagina.

LEMASTER, Evanston, Ill.

GROWTH AND THE ECONOMIC DEPRESSION. CARROLL E. PALMER, Pub. Health Rep. **48**:1277 (Oct. 20) 1933.

This study was undertaken for the explicit purpose of determining whether or not the weight of elementary school children in Hagerstown, Md., differs today in significant particulars from the weight of children of the same age and sex living in the same city during the past decade. Analysis of the data collected showed that the average weight of children in 1933 presented no statistically significant difference from the weight of children from 1921 to 1927. The variability of body weight was not consistently different for the two periods in boys, but in girls the body weight was slightly more variable in 1933. Classification of the children weighed in 1933 into three groups, those (1) from families of the unemployed, (2) from families of the part time employed and (3) from families of the regularly employed, shows approximately the same differences as are generally found between children from different socio-economic classes. It is concluded, therefore, that there has been no obliteration or widening of class differences during the period of economic depression. A separate classification of the children into two groups, of those receiving aid from the charities and those not receiving such aid, shows that children in the first group are from 2.5 to 9 pounds (1,134 to 4,082 Gm.) lighter, on the average, than those in the latter group. It is inferred that those children who are most in need of supplementary aid are probably receiving it.

LEMASTER, Evanston, Ill.

A CASE OF DEAFNESS DUE TO RICKETS. MACLEOD YEARSLEY, Brit. J. Child. Dis. **30**:194 (July-Sept.) 1933.

The title of this article is misleading, as there is no definite evidence that the deafness of this 4½ year old child was caused by rickets. The child is said to have been in an infirmary for seven or eight months during the first year suffering from "acute rickets," and, according to the mother, returned home "stone deaf." On examination the tympanic membranes exhibited the characteristic "salmon reflex" usually associated with the classic otosclerosis of Denket. Toward the end of the article appears the statement that "since in cases of deaf-birth, similar changes in the petrous bone have been found, it may well be that in the case above described, there exists a link between some forms of congenital deafness and otosclerosis."

LANGMANN, New York.

CLINICAL TESTS OF THE ANTIRACHITIC ACTIVITY OF CALCIFEROL. J. C. SPENCE, Lancet **2**:911 (Oct. 21) 1933.

Pure vitamin D in crystalline form was isolated simultaneously by workers in England, who gave it the name "calciferol," and by workers in Germany, who called it "vitamin D_2." Twelve actively rachitic children were treated with daily doses of the pure vitamin D for eleven weeks or more. The therapeutic effects were estimated by serial roentgenograms, which were compared with a standard scale of the optimal rate of cure. It was found that the pure vitamin D had an active curative effect on the rickets and that it produced healing at an optimal rate, acting as quickly and as effectively as the usual therapeutic doses of cod liver oil or viosterol.

LANGMANN, New York.

THE VITAMIN D POTENCY OF SUN-IRRADIATED DRIED YEAST. KATHERINE H. COWARD, Lancet **2**:920 (Oct. 21) 1933.

From her experiments Coward concludes that yeast may be activated against rickets by exposure to strong sunlight, and that different samples of dried yeast may differ greatly in the extent to which they may thus be activated.

LANGMANN, New York.

FAT METABOLISM IN MALNUTRITION. H. DORLENCOURT, Nourrisson **21**:221 (July) 1933.

Undernutrition affects, first, the carbohydrates; second, the fats, and finally, the proteins. The fatty tissue disappears in regular order, beginning with the subcutaneous layer of abdominal fat; the last fat to disappear is that of the face. When the athrepsia becomes so severe that death threatens, only from 6.75 to 9 per cent of the normal amount of fat remains. The fats containing the largest percentages of olein have the lowest melting points and are the first to be metabolized, and conversely those containing the smallest amounts of unsaturated fatty acids survive the longest. A table gives the analysis of fats from different parts of the body and the order in which they disappear.

McCLELLAND, Cleveland.

THE SYNDROME OF FETID COLIC IN INFANTS. P. NOBÉCOURT, Paris méd. **2**:357 (Nov. 3) 1933.

Nobécourt applies this term to a syndrome of fetid breath, digestive troubles and various general symptoms. The fetid odor is one of putrefaction. The stools usually number two a day and are soft, yellow, very putrid and full of undigested material. The abdomen shows nothing unusual unless occasionally a spastic colon. Generalized pain is common. The general symptoms are coated tongue, anorexia, gastric vomiting, pallor and loss of weight. The condition is essentially chronic, and usually appears in the latter part of the first year or in the second year. The origin is always in some dysfunction of digestion, perhaps initiated in infancy by a faulty diet. The treatment consists in stimulating the intestinal secretion by alkalies, cleansing the intestine by giving cultures of lactic acid bacilli, supplying missing secretions such as pepsin, hydrochloric acid and enterokinase and combating spasm by cold or hot compresses and constipation by saline laxatives.

SANFORD, Chicago.

ADVANTAGES AND DISADVANTAGES OF MILK STERILIZATION (CLINICAL AND EXPERIMENTAL STUDY). W. CATEL, Deutsche med. Wchnschr. **59**:1689 (Nov. 10) 1933.

Catel coined the word *Anschlagswert*, by which he means the gain per kilogram of weight per day in grams divided by the calories of food intake per kilogram of body weight. If this quotient is high it means that the food in question is well utilized by the specific animal or human subject. If the quotient is low it means that the food administered is not well utilized. He found that, measured by the *Anschlagswert*, the milk of an animal is invariably better utilized by an offspring of its own kind when raw than when sterilized or autoclaved. However, the same milk given to the young of other animals, for instance, cow's milk to goats, is better utilized if sterilized. As a rule, autoclaving the milk caused marasmus and finally cachexia.

The feeding of any kind of milk sterilized by heat often causes other complications besides poor gain. It might produce diarrhea, secondary respiratory infections and, in some cases, even spasmophilia. These untoward consequences could not be avoided by delaying the destruction of vitamin C by making the milk acid before boiling. Studies in metabolism were carried out on goats fed sterilized goat's milk. It was found that severe disturbances occurred in the mineral

metabolism and that the proteins, fats and carbohydrates were not as well utilized as when the milk was administered raw.

The addition of vitamins in the form of yeast, lemon juice and vegetables often cleared up the disturbances in growth produced by feeding boiled milk. Even the damages done by feeding autoclaved milk can be considerably repaired by the addition of vitamins. As it is not advisable to feed babies raw milk, because of the danger of infection by Bacillus coli and tuberculosis bacilli, a short boiling immediately before use is most desirable. If the milk cannot be used immediately after this short boiling, a thorough sterilization according to the Soxhlet method is preferable.

KERESZTURI, New York.

EXPERIENCE WITH DIET OF RAW APPLES IN INTESTINAL DISORDERS. A. HARTWICH, München. med. Wchnschr. **80**:1217 (Aug. 4) 1933.

Moro was the first to investigate systematically Heisler's observation that a diet of raw apples could cure diarrhea. Heisler had his attention drawn to this possibility by one of his patients who had stopped a diarrhea of several weeks' duration by eating fruit. The treatment of diarrhea with a diet of apples has been used mostly by pediatricians. Hartwich has found it equally effective in forty-six adult patients with acute intestinal disorders of various etiology. The diet of apples is given for one or two days. The diarrhea stops promptly, the temperature drops and, if pathogenic organisms were present in the stools, these disappear in from three to seven days.

BRAHDY, Mount Vernon, N. Y.

APPLE DIET IN THE TREATMENT OF CHRONIC FERMENTATIVE DYSPEPTIC ENTERITIS. P. BOGDANOVIE, München. med. Wchnschr. **80**:1217 (Aug. 4) 1933.

Many patients with chronic fermentative dyspeptic enteritis have failed to obtain relief from the usual methods of treatment. In chronic fermentative dyspeptic diarrheas there is primarily a derangement in the digestion of carbohydrates. The stools contain undigested starch, an increased amount of fat and some undigested muscle fibers. Bogdanovie has had unusual success by treating these patients with the apple diet. Raw or baked apples with a little tea and lemon are the sole diet for two days. The apples must be thoroughly chewed. After two days other foods are gradually added, such as boiled or broiled lean meat, meat broth, eggs and bananas. Later, noodles and macaroni are added and, after two weeks, vegetables. He thinks that the beneficial results with the apple diet are due to the adsorption effect, the fruit acids and the vitamins.

BRAHDY, Mount Vernon. N. Y.

APPLE DIET IN INFANTS AND SMALL CHILDREN. E. URBANITSKY, München. med. Wchnschr. **80**:1219 (Aug. 4) 1933.

The good results obtained by Urbanitsky with the Heisler-Moro diet of apples in children with diarrhea induced her to try it with infants and young children. Since suitable apples for the diet are not available during the entire year, especially during the summer, she used a prepared apple powder (Aplona). She treated ten infants under 6 months, twelve under 1 year and twenty-five under 2 years of age. Diarrheas of various types, of both enteral and parenteral etiology, responded equally well. The infants were first given tea with a 4 per cent apple powder, 100 Gm. six times a day. Then they received a milk mixture, with from 5 to 6 per cent apple powder in place of sugar. The sugar gradually replaced the powder after four days. In the most severe cases the stools became pasty, and the loss of weight stopped in two or three days. The stools were normal in three or four days. The number of calories was reduced to about one half during the treatment in the severe cases and to about two thirds in the milder cases. Patients with intoxication received gradually increasing amounts of protein milk in addition to the apple diet after the first day.

BRAHDY, Mount Vernon, N. Y.

LACTIC ACID AND CITRIC ACID WHOLE MILK IN INFANT FEEDING. E. LYDTIN München. med. Wchnschr. **80**:1321 (Aug. 25) 1933.

Lydtin found acidified whole milk a more satisfactory feeding for infants than any of the other preparations of milk which he has tried at the Munich Children's Hospital. He uses acidified whole milk when there is need of a feeding of high caloric value but of minimum volume. He also prescribes it for dystrophic, atrophic and premature infants, as well as those with mild acute diarrhea (dyspepsia). For severe diarrhea with intoxication the first feedings are breast milk, and after the toxic symptoms subside acidified milk is given. Other indications are anorexia, hyperpyrexia (in pneumonia or pyuria) and pylorospasm. By using acidified milk as a complemental feeding for a breast fed infant he has found weaning easier. He believes that it is the best food for infants next to breast milk.

BRAHDY, Mount Vernon, N. Y.

THE DISTRIBUTION OF FATTY TISSUE ON THE SURFACE OF CHILDREN'S BODIES. SHIRO OGAWARA, Ztschr. f. Konstitutionslehre **17**:90 (Oct. 26) 1932.

This is the report of an elaborate and valuable study of more than one hundred children in the pathologic institute of the Vienna City Hospital. It does not lend itself to advantageous abstracting. VINTON, Brooklyn.

HYDROGEN ION CONCENTRATION OF DUODENAL JUICE IN CASES OF ACUTE INDIGESTION IN INFANTS. O. K. KRIKENT, Pediatriya **14**:33, 1930.

It has been established in considerable work on blood by Rosenbaum, Sheer and Demert that there is a definite increase in gastric acidity in cases of acute indigestion. In regard to the duodenal juice there are the investigations of Rudnoff. Children suffering from indigestion give a weakly acidic reaction, with a p_H from 6 to 7, while healthy children show a variation of p_H from 6.4 to 7.2. A child, 2½ months old, in a condition of marked atrophy, showed a p_H of 6.8. With the appearance of indigestion and diarrhea it decreased to 6.4. In children convalescent after intoxication the reaction remained weakly acidic at from 5.4 to 5.8. Schoff, Eliasberg and Mosse found in breast fed children a p_H of from 6.8 to 7.6; in the majority of cases a p_H slightly higher than 7 was found and, rarely, up to 8.2. In poorly nourished children suffering from indigestion with an invasion by Bacillus coli, the p_H was found to be 5.6, and in one case it was as low as 3.2.

Morrow and Sheer attributed considerable importance to the change of the hydrogen ion concentration in the small intestine as the cause of indigestion due to endogenous infection and abnormal chemical processes as a result of the invasion by B. coli. There is a prevalent opinion that favorable conditions for the multiplication of intestinal bacteria will cause the p_H to fall below 4.6. Zekhenstatt found a considerable number of intestinal bacteria two and one-half hours after feeding ordinary milk to children suffering from dietary disorders. The introduction of human milk hinders the multiplication of the bacteria.

It may be generally said that in both acute intoxication and chronic dyspepsia in children suffering from marked dystrophies the p_H falls below 7.4.

YAMPOLSKY, Atlanta, Ga.

Prenatal Conditions

OXYCEPHALY IN BROTHERS. M. R. SAWHNEY, Brit. J. Ophth. **18**:169 (March) 1934.

The ages of the boys were 5 and 11 years. The symptoms were the same in both: fairly typical oxycephaly with high palatal arches and fairly well marked bilateral exophthalmos and ptosis. The lids could not be raised voluntarily. The eyeballs were fixed in the middle line, and there was complete inability to move

the eyes in any direction. The immobility was not due to the exophthalmos. The fundus, vision and fields were practically normal. There were two other boys and two girls in the family. They and the parents were normal. The article is illustrated.

ZENTMAYER. [ARCH. OPHTH.]

CONGENITAL HYDROPS. ANDÉRODIAS, DUPÉRIÉ, MAHON and DUBARRY, Bull. Soc. d'obst. et de gynéc. **22**:501 (June) 1933.

The authors comment on the rarity of this disease in France as compared with Germany, suggesting that a racial factor may be involved. They report two cases. In the first, the infant weighed 3,800 Gm. at birth and died immediately afterward. In the second, the infant weighed 4,000 Gm. and lived forty hours. At autopsy the infants presented the typical syndrome of congenital generalized edema with erythroblastosis. A brief discussion of the disease is given.

GLASER, Rochester, N. Y.

LEFT CONGENITAL DIAPHRAGMATIC HERNIA. BAAKLINI and CHÉDID, Bull. Soc. de pédiat. de Paris **30**:691 (Dec. 20) 1932.

A boy, aged 2 years and 3 months, was suddenly taken ill. The chief disorder was incessant vomiting. The only positive physical finding was marked displacement of the heart to the right. Roentgen examination confirmed this and also showed a rounded shadow of increased density in the left lower half of the thorax, extending from the level of the diaphragm to the sixth intercostal space; a sip of barium sulphate demonstrated that the stomach was present in this dense shadow. The diagnosis was clearly diaphragmatic hernia. An operation was performed, and a large patency admitting the whole fist was found in the diaphragm on the left side. The stomach, large intestine and part of the omentum as well as the spleen were located in the thorax. These organs were replaced in the abdomen, and the hernial orifice was closed. The child went into collapse, but was revived. He died five hours after the operation.

BENJAMIN, Montreal, Canada.

A CASE OF RETROGRADE THORACO-ABDOMINAL STRANGULATED CONGENITAL DIAPHRAGMATIC HERNIA. DEROME, BOPPE, GRÈZE and BAILLARGÉ, Bull. Soc. de pédiat. de Paris **30**:695 (Dec. 20) 1932.

A boy, aged 12 years, was seized with acute abdominal pain. He had been perfectly well until the onset of the present illness. He sank rapidly and died before a diagnosis was made. At autopsy it was observed that the left half of the thorax contained the stomach and the entire intestinal tract as far as the descending colon. Part of the fundus of the stomach was gangrenous and had a perforation from which gastric contents exuded. Strangulation of this part of the stomach in the hernial orifice had occurred, and the remainder of the stomach above the ring of strangulation was in the thorax. The opening in the diaphragm was crescentic and was situated to the left of and behind the left lobe of the liver. There was no hernial sac. The spleen was in the abdominal cavity. The left lung was markedly atelectatic and weighed 50 Gm. The heart was displaced to the right. A photograph of the thoracic and abdominal cavities laid open with the organs in situ is shown. It is pointed out that strangulated retrograde diaphragmatic hernia with the viscus caught in its descent from the thorax into the abdomen is rare.

BENJAMIN, Montreal, Canada.

CONGENITAL OBSTRUCTIVE JAUNDICE IN AN INFANT. AXENTE IANCOU, M. SIRETEAUNOU and L. P. DARIOU, Bull. Soc. de pédiat. de Paris **30**:699 (Dec. 20) 1932.

A boy, 6 weeks old, was markedly jaundiced. The jaundice appeared on the fourth day after birth and became progressively worse. The urine contained bile,

and the stools were white and did not contain bile since the onset of jaundice. The liver was considerably enlarged, and the spleen was palpable. The tuberculin reaction and the Wassermann reaction of the blood were negative. The blood showed moderate anemia. There was apparently some malformation of the biliary tract. Operation was advised, but the parents refused to have it performed. The infant died after three weeks of hospitalization. No autopsy was done.

BENJAMIN, Montreal, Canada.

MALFORMATIONS OF THE LOWER PART OF THE BODY. E. NACHMANSOHN, Frankfurt. Ztschr. f. Path. **44**:117, 1932.

A stillborn child is described, measuring 36 cm. In place of the lower extremities there was a tail-like structure 10 cm. in length, taking origin from the pelvic region and becoming gradually smaller, to end in a finger-like projection. The external genital organs and the anus were missing. In the region of the lowest portion of the lumbar segment was a small soft projection 1.4 cm. in length, which did not reveal an opening. Only one umbilical artery could be found. No urinary bladder, urachus or persistent cloaca could be made out. The lower portions of the abdominal muscle were markedly hypoplastic. The large intestines were distended and filled with meconium, and the sigmoid colon ended blindly. The surfaces of the serosa were smooth and glistening. Both suprarenal glands, were present and normally located, but the kidneys were absent. Close to the umbilical artery two gonads were found, which resembled testes. There was also an occult spina bifida. The explanations for these malformations are given. The author recommends the following classification of malformations of the lower part of the body: (*a*) isolated defects of the external form of the caudal portion of the body, (*b*) isolated defects of the anlagen of the inner organs of the caudal end of the body and (*c*) isolated defects of the external form of the caudal portion of the body (1) with normally formed and developed inner organs and (2) with defects of the inner organs. This classification does not seem justifiable because (*a*) and (1) overlap.

SAPHIR. [ARCH. PATH.]

Diseases of the New-Born

PREVENTION AND TREATMENT OF ASPHYXIA IN THE NEWBORN. LOUISE MCILROY, M. J. & Rec. **138**:455 (Dec. 20) 1933.

As a result of research into the causes of fetal death, it was found that the blades of the forceps should be applied in the biparietal diameter, with the head as near complete flexion as possible. Too rapid extraction of the head should be avoided. Delivery should be slow, and no undue traction should be permitted. The new-born baby should have its mouth wiped out at once. It should be kept warm. No undue traction on the cord should be allowed.

In caring for an asphyxiated child, all violent forms of artificial respiration should be avoided. The best artificial respiration is the application of the mask and the giving of carbon dioxide in oxygen. Mucus should be aspirated from the mouth before artificial respiration. Hot or cold baths should not be given, but the child should be kept warm and quiet.

WILLIAMSON, New Orleans.

FETAL BIRTH INJURIES WITH SPECIAL REFERENCE TO INTRACRANIAL LESIONS. P. BROOKS BLAND, West Virginia M. J. **30**:9 (Jan.) 1934.

All the tissues and organs of the body are subject to possible injury during birth. Injuries of the cerebrospinal system are the most frequent and the most serious of all fetal injuries at birth.

In this country about 150,000 infants are born dead or die soon after birth; about one third of these deaths are due to intracranial injuries. Intracranial hemorrhage in connection with birth occurs much more frequently than is generally supposed. The most frequent location of intracranial injury is the tentorium, just below its union with the falx.

Etiologic factors predisposing to intracranial damage are: prolonged and difficult labor, technically difficult and imprudent deliveries with forceps, complicated breech deliveries, especially with hasty and unskilled delivery of the aftercoming head, prematurity and immaturity, difficult delivery of the aftercoming head in versions and chemical changes of the blood and constitutional diseases.

Methods of preventing intracranial injury are summarized as follows: scrupulous antenatal supervision, evasion, so far as possible, of difficult manual and instrumental deliveries, giving preference to abdominal delivery, avoidance of hasty, antiquated means of delivering the aftercoming head in cases of breech presentation, the routine employment of the Piper forceps in delivery of the aftercoming head in cases of breech presentation and version, repetition of spinal paracentesis in infants showing free blood in the spinal fluid and the intragluteal injection of from 10 to 20 cc. of human blood in all cases in which there are signs of intracranial hemorrhage or trauma.

SHAWKEY, Charleston, W. Va.

A CONTRIBUTION TO THE STUDY OF ERYTHROBLASTOSIS: ICTERUS GRAVIS NEONATORUM. J. C. HAWKSLEY and REGINALD LIGHTWOOD, Quart. J. Med. **3**:155 (April) 1934.

A clinical and pathologic study of eighteen cases of icterus gravis neonatorum is presented from the Hospital for Sick Children, Great Ormond Street, London. The subject is discussed under the following headings: clinical features, differential diagnosis, changes in the peripheral blood, morbid anatomy and pathology, etiology, treatment and prognosis and sequelae.

The authors conclude that evidence exists that brings the condition into close relationship with hydrops foetalis and hemolytic anemia. The changes in the blood consist in rapidly forming hemolytic anemia. The hematopoietic system is intensely stimulated and responds with the outpouring of nucleated red cells, producing an embryonic blood picture. There is extramedullary hematopoiesis; the bone marrow shows immaturity and regenerative activity. Cellular degeneration and necroses occur in the liver and brain in certain cases. Anemia and certain nervous manifestations occur as sequelae. The treatment is discussed, and the value of repeated blood transfusions is emphasized.

The authors believe that a hemolytic process is more likely to be primary than is a disturbance of blood formation. They do not believe that there is sufficient evidence to incriminate any certain toxin as the causative factor.

Abstracts of clinical and anatomic records, a rather complete bibliography and excellent photomicrographs are presented.

BRADFORD, Rochester, N. Y.

Acute Infections

DISTRIBUTION OF THE VIRUS OF POLIOMYELITIS IN THE CEREBROSPINAL AXIS OF MONKEYS. M. BRODIE, J. Immunol. **25**:71 (July) 1933.

The distribution of poliomyelitic virus throughout various levels of the central nervous system following intracerebral inoculation was studied in monkeys. The infectivity of the cord, medulla and pons was much greater than that of the midbrain, cerebrum and cerebellum. A relationship was demonstrated between infectivity and destruction of the nerve cells in various levels during the acute stage of the disease. The cerebral cortex was less effective in the production of active immunity than was the tissue of the cord.

FOTHERGILL, Boston.

MANAGEMENT BY MECHANICAL RESPIRATOR OF POSTDIPHTHERITIC RESPIRATORY PARALYSIS. J. E. GORDON, D. C. YOUNG and F. H. TOP, J. Pediat. **3**:580 (Oct.) 1933.

Of the 5,057 persons with diphtheria admitted to the wards of the Herman Kiefer Hospital, Detroit, since 1927, 632 died. Among the latter were 13 of 21

patients with diaphragmatic and intercostal paralysis. Respiratory paralysis developed four or more weeks after the onset of diphtheria and usually in the wake of paralyses involving the palate, eyes, larynx, pharynx and extremities. Two patients with respiratory paralysis were placed in the Drinker respirator. The authors believe that the early use of the Drinker respirator would reduce the mortality caused by this uncommon but serious complication of diphtheria.

LEMASTER, Evanston, Ill.

VULVOVAGINAL DIPHTHERIA. MARK J. WALLFIELD and ABRAHAM M. LITVAK, J. Pediat. **3**:756 (Nov.) 1933.

A case is reported of tonsillar diphtheria with secondary diphtheritic vulvovaginitis in a 7 year old girl. Recovery was rapid after antitoxin was administered. The literature concerning diphtheritic vulvovaginitis is briefly reviewed.

LEMASTER, Evanston, Ill.

THE PROBLEM OF OTITIS MEDIA AND MASTOIDITIS IN SCARLET FEVER. JACOB I. ABRAMS and SAMUEL FRIEDMAN, New England J. Med. **209**:494 (Sept. 7) 1933.

Among the 4,215 persons with scarlet fever admitted to the South Department of the Boston City Hospital from 1928 to 1932, there were 574, or 13.6 per cent, who had purulent otitis media. Of these, 60 entered the hospital primarily for mastoidectomy. An analysis based on the total number of cases of otitis media shows practically 91 per cent occurring in the first decade of life. The peak is reached in the group 1 year of age, in which otitis media is seen to develop in almost 1 of every 2 patients (45). The percentage gradually falls until, in the third decade, it is only 1.9. The highest incidence of otitis media, both relatively and absolutely, occurs during the first four months of the year. The time of onset is: first week, 35 per cent; second week, 25.4 per cent; third week, 15.1 per cent; fourth week, 9.9 per cent; after the fourth week, 14.6 per cent.

Among the 574 cases, 210 were on the right side, 153 on the left and 211 were bilateral. The onset in some cases was painless and without symptoms, and a discharge of pus was the first indication. Frequent otoscopic examinations are essential.

Practically all authors agree on the importance of early myringotomy. The average duration of drainage from ears in which the drum was incised was twenty-two and two-tenths days and that of drainage from ears in which the drum ruptured spontaneously was twenty-eight days. In 26.7 per cent of the ears involved, the drum was incised, and in 63.3 per cent it opened spontaneously. Of the mastoidectomies, 25.3 per cent followed incision of the drum and 74.7 per cent followed spontaneous rupture of the drum, so that 14.3 per cent of the ears in which the drum was incised required a mastoidectomy, as compared with 24.1 per cent of the ears in which the drum ruptured spontaneously.

The youngest of the patients in whom mastoidectomy was performed was aged 5 months. There were 93 males (56 per cent) and 74 females (44 per cent). Among the 166 operations, 73 were on the right side, 53 on the left and 40 were bilateral. Of the 155 cases classified, 75 were in the group of acute involvement (first four weeks) and 80 were in the group of chronic infection. For the 75 in the first group, the average duration from the onset of otorrhea to the mastoidectomy was twelve and a half days; for the 80 in the second group, the average duration was forty-three and seven-tenths days. In the first group, the average duration of postoperative fever was five days; 18 per cent of the patients in this group had no increase in temperature. In the second group, the average duration of postoperative fever was only one and seven-tenths days; 48 per cent had no fever.

Among the 166 patients on whom mastoidectomy was performed, 9 required tying of the jugular vein for lateral sinus thrombosis. Two of these patients died, one of septicemia and septic endocarditis and the other of meningitis due to

Streptococcus haemolyticus. There were also 6 other deaths in the group with mastoiditis, a total of 8 deaths, making a case mortality of only 4.8 per cent. Only 1 of these deaths was in the so-called chronic group. The authors believe that the chronic otitis media and deafness due to scarlet fever might be much curtailed by the performance of mastoidectomy at the proper time. GENGENBACH, Denver.

CURRENT PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES, AUGUST 13-SEPTEMBER 9, 1933. Pub. Health Rep. **48**:1189 (Sept. 29) 1933.

The number of cases of poliomyelitis increased from 667 for the preceding four weeks to 1,412 for the four weeks from August 13 to September 9. The incidence of scarlet fever was 4,380, which is the highest incidence reported for this period during the past five years. The number of cases of typhoid fever was considerably below the level of recent years. The incidence of smallpox, influenza, meningococcic meningitis, diphtheria and measles continued favorably at low levels.

LEMASTER, Evanston, Ill.

CURRENT PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES, SEPT. 10 TO OCT. 7, 1933. Pub. Health Rep. **48**:1309 (Oct. 27) 1933.

For the country as a whole the number of cases of poliomyelitis decreased from the four weeks preceding September 10, but still remained considerably in excess of the number for 1932 and more than twice the number reported for this period in 1929. The incidence of meningococcic meningitis and typhoid fever was the lowest for this period in recent years. Cases of measles and influenza were reported in about the same numbers as in the past few years. Reports on diphtheria indicated only a normal seasonal increase. Deaths from all causes in large cities were 9.8 per thousand inhabitants.

LEMASTER, Evanston, Ill.

CURRENT PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES: OCT. 8 TO NOV. 4, 1933. Pub. Health Rep. **48**:1417 (Nov. 24) 1933.

The number of cases of poliomyelitis dropped from 1,271 for the four weeks preceding October 8 to 602 for the four weeks ending November 4. Each geographic area showed a decline. During this period the incidence of influenza increased about 50 per cent, but still remained considerably below the level of 1932. The incidence of scarlet fever and diphtheria was slightly higher than for the corresponding period of recent years. The number of cases of measles, meningococcic meningitis, typhoid fever and smallpox continued low. Deaths from all causes in large cities averaged 10.6 per thousand inhabitants.

LEMASTER, Evanston, Ill.

INFLUENCE OF PIGMENTATION DUE TO LIGHT TREATMENT ON THE ERUPTION OF MEASLES. ROBERT AITKEN, Brit. J. Phys. Med. **7**:241 (March) 1933.

Measles developed in a patient after four weeks of ultraviolet irradiation. The rash was much more intense in areas which had been exposed. Aitken believes that the localization was due to the pigmentation rather than to the light.

HARTMAN, Cleveland.

THROMBOPHLEBITIS IN ACUTE RHEUMATISM. C. BRUCE PERRY, O. C. M. DAVIS and BERNARD SCHLESINGER, Lancet **2**:966 (Oct. 28) 1933.

A review of the literature leads the authors to remark that apart from Poynton's reports the question of rheumatic phlebitis received scant attention since 1900. Three cases of venous thrombosis are described, two of them occurring in girls of 11 and 13 years of age and the third in a man of 20. At postmortem examina-

tion of the 11 year old girl, an adherent thrombus was found completely occluding the left subclavian, the left internal jugular and the left innominate vein. On histologic examination, the thrombosed veins showed loose collections of cells throughout the media. These cells appeared to be of connective tissue origin. When such cells were grouped in the vicinity of a vessel, they formed nodules which closely resembled the Aschoff nodules of the myocardium. Examination of the heart revealed typical rheumatic endocarditis and myocarditis. From the clinical features and the histologic observations the authors conclude that rheumatic phlebitis may occur as a rare feature of rheumatism, and that the venous thrombosis met with during acute rheumatism is secondary to rheumatic phlebitis.

LANGMANN, New York.

DIPHTHERIA IN HULL AND ITS RELATION TO BACTERIOLOGICAL TYPE. H. MASON LEETE, J. W. MCLEOD and ANDREW C. MORRISON, Lancet **2**:1141 (Nov. 18) 1933.

Diphtheria in Hull during the past three years has been particularly severe. Deaths per hundred thousand were 30.8, whereas, in all county boroughs the figure was only 9.8. Of 310 cases of all grades of severity, 59 per cent showed the gravis strain of the diphtheria bacillus. Of the forty toxic deaths in this series, thirty-five were due to the gravis strain. The striking feature of an infection with this strain in a completely nonimmune subject is the extremely rapid course of the toxemia. The short interval of time between infection and fixation of the toxin defeats the ordinary methods of recognition and treatment.

LANGMANN, New York.

HEMATOLOGY OF WHOOPING COUGH. D. MORITZ and L. LACKNER, Arch. de méd. d. enf. **36**:669 (Nov.) 1933.

Early diagnosis of whooping cough is considered a vital desideratum, not only in the interest of the patient, but in the prevention of transmission to others. To differentiate pertussis from other spasmodic conditions of the respiratory tract, such as bronchial catarrh, tracheobronchial adenopathy and acute laryngitis, hematologic studies are imperative. In addition to the well known lymphocytosis, Rohr and Krieger have demonstrated that there is a much slower sedimentation of the red cells than obtains with other infections. The authors discuss their experience with sixty-five patients, fifteen of whom were nurslings; the clinical course was divided into three phases, the first corresponding to the catarrhal stage, the second embracing the period of paroxysms, and the third representing the stage of decline or, as Hamburger describes it, the neuropsychogenic period. In the first stage in this series there was a lymphocyte count ranging from 7,800 to 15,000; during the second stage it averaged 19,000, and in the third, 7,800. There was a moderate slowing in the sedimentation of the red cells in only 25 per cent of the cases.

AMESSE, Denver.

MALIGNANT DIPHTHERIA IN A CHILD WHO HAD BEEN IMMUNIZED WITH RAMON'S ANATOXIN. JEAN PIGOT, Bull. Soc. de pédiat. de Paris **30**:505 (Oct. 18) 1932.

A girl, 7 years old, received three doses of anatoxin of 0.5, 1 and 1.5 cc. respectively, at intervals of three weeks. Two years later malignant diphtheria developed and despite enormous repeated doses of antitoxic serum the child died. The culture from the throat showed long diphtheria bacilli and cocci in chains. There is no mention made of a Schick test after the immunization.

BENJAMIN, Montreal, Canada.

INDICATIONS FOR ANTITYPHOID VACCINATION IN THE INFANT. L. TANON and H. CAMBESSEDES, Rev. franç. de puériculture **1**:79 (May) 1933.

The arguments against antityphoid vaccination in infants and children, that typhoid occurs infrequently in children and that children have greater resistance to the infection, do not hold. Statistics from Belgrade and Paris show that the number of cases in infants and small children is smaller than that of cases in adults, but that it is by no means negligible. The greatest number of cases occur in persons between fifteen and twenty years of age. Allergy determinations show that resistance to the infection is minimal in infancy and develops slowly until, at about the fifteenth year, it approaches that of the adult.

CRANE, Chicago.

STATISTICAL STUDY OF DIPHTHERIA AT AMEDEO DI SAVOIA HOSPITAL, TORINO, ITALY. AMOS FOA, Pediatria **41**:28 (Jan.) 1933.

Desiring to develop definite conclusions concerning therapy with antidiphtheritic serum, the author made a detailed study of patients thus treated at the Amedeo di Savoia Hospital, Torino, from 1924 to 1931. Altogether, 1,128, whose condition was bacteriologically diagnosed as diphtheria are included in the report. The

Therapeutic Advantages of Early Administration of Serum

Number of Patients	Day of Disease Serum Was Injected	Number Cured	Number Who Died	Percentage of Mortality
3	1	3	..	0
363	2	334	29	8
498	3	445	53	11
175	4	127	46	27
51	5	34	17	33
18	6	9	9	50
9	7	4	5	55
6	8	3	3	50

patients were admitted during a period of eight years, the average number admitted annually being 141, and were from 1 year of age (8.5 per cent) to over 11 years of age (16.4 per cent), the highest number being between the ages of 6 and 10 years (24.4 per cent).

The location of lesions is set forth as having been: pharyngeal 624 (55.3 per cent); nasal 9 (0.8 per cent); laryngeal 411 (36.3 per cent); mixed 76 (6.9 per cent); conjunctival 7 (0.6 per cent); buccal (lower lip) 1 (0.09 per cent).

In the course of treatment 293 intubations and 18 tracheotomies were performed, with bronchopneumonia developing in 60 per cent of the patients intubated. Of the 18 patients tracheotomized 85 per cent contracted bronchopneumonia; this group yielded a mortality of 29 per cent. The author considers intubation far superior to tracheotomy. The general mortality from diphtheria (in the hospital named) was 14.7 per cent.

The author discusses in detail the increased efficacy of early administration of serum from the standpoint of cures and reduction of complications, and concludes that "serum therapy in diphtheria is most efficacious and that to neglect its use is the assumption of a most serious responsibility."

SIGNORELLI, New Orleans.

CLINICAL STATISTICS AND AN EPIDEMIOLOGIC STUDY OF AN EPIDEMIC OF MEASLES. L. MOLINARI, Pediatria **41**:1272 (Oct. 1) 1933.

Molinari reports in detail a study based on observations in the hospital for contagious diseases in Venice during an epidemic in which many children were stricken simultaneously with measles and diphtheria. He believes that the patients

were primarily diphtheria carriers in whom the advent of measles, by reducing the general resistance, provoked favorable conditions for the manifestation of diphtheritic symptoms. He points out the extreme gravity of such an association of diseases and explains the malignancy of this epidemic in comparison with preceding epidemics of measles.

SIGNORELLI, New Orleans.

THE POLYVALENCY OF THE ANATOXIN OF DIPHTHERIA (TOXOID). ESPEDITO DI LAURO, Pediatria **41**:1402 (Nov.) 1933.

Experimental research by Di Lauro at the Istituto d'Istologia e Fisiologia Generale of the Royal University of Naples showed that the anatoxin of Ramon (toxoid) possesses a specific prophylactic power against the poison of the viper, although it does not possess any curative value against it. Thus, its prophylactic value being proved against diphtheria also, makes the product a polyvalent one. The author proposes to continue his research, hoping to discover whether this polyvalence is still further multiple.

SIGNORELLI, New Orleans.

CARRIERS OF INFLUENZA BACILLI. A. KAIRIES, Arch. f. Hyg. **111**:1 (Oct.) 1933.

Kairies agrees with Pfeiffer that the influenza bacillus is not ubiquitous, certainly not in the sense that the colon and hay bacilli, staphylococci, certain types of pneumococci, streptococci and the gram-negative cocci commonly found in the respiratory passages are considered ubiquitous. Adults may carry and discharge influenza bacilli for many years. Children are in constant danger from such carriers, and outbreaks of grip among children may be attributed to the presence of these carriers.

GLASER, Rochester, N. Y.

UNDULANT FEVER IN SMALL CHILDREN. W. HAUPTMANN and KONRAD EBERLE, Arch. f. Kinderh. **100**:65 (Sept. 29) 1933.

The literature concerning Bang's disease in infants and small children is reviewed briefly and a case in a girl, 3½ years old, is reported. This patient was infected from drinking raw milk. A positive blood culture and agglutination were obtained.

LEMASTER, Evanston, Ill.

ACTIVE PROTECTIVE INOCULATION AGAINST VARICELLA. ZOTTÁN VON GULÁCSY, Arch. f. Kinderh. **100**:75 (Sept. 29) 1933.

Twelve susceptible children exposed to varicella were given an intracutaneous injection of a small quantity of clear fluid taken from a vesicle of varicella and diluted in salt solution. No local or systemic reaction was observed. Of these children, only two developed varicella, which was very mild, while all of the uninoculated controls contracted typical varicella of moderate severity. Following the protective inoculation, the basophils and plasma cells of the blood increased, simulating the blood picture during the period of incubation of varicella.

LEMASTER, Evanston, Ill.

OBSERVATIONS ON MALIGNANT DIPHTHERIA. A. STROÉ, Arch. f. Kinderh. **100**:86 (Sept. 29) 1933.

In several cases of malignant diphtheria, ulcerated necrotic areas were seen on the mucosa near the diphtheritic membrane. Cultures revealed numerous anaerobic bacteria. In treating these cases excellent results were obtained by injecting both diphtheria antitoxin and antigangrene serum. Stroé is strongly of the opinion that the clinical picture of malignant diphtheria is frequently caused by simultaneous infection with anaerobic bacteria and diphtheria bacilli.

LEMASTER, Evanston, Ill.

CLINICAL CONTRIBUTIONS TO THE KNOWLEDGE OF GONORRHEA IN CHILDHOOD. PART IV. LÁSZLÓ V. DOBSZAY, Arch. f. Kinderh. **100**:106 (Sept. 29) 1933.

In judging whether or not a case of gonorrheal vulvovaginitis in a child is cured, Dobszay considers the results of three procedures: (1) clinical observation for one year with frequent endoscopic examinations; (2) provocative tests with silver nitrate, copper sulphate and compound solution of iodine, and (3) cutaneous tests with gonococcus vaccine. When gonococci persist for a long time, the child may be a carrier of gonococci, the constitutional condition may be at fault, reinfection may have occurred, or undiscovered and untreated foci may be the origin of continual infection.

LEMASTER, Evanston, Ill.

THE ALLERGY THEORY OF VARICELLA WITH A CASE OF ENCEPHALITIS AND SEVERE BILATERAL CHOKED DISK. E. MAYERHOFER and J. BREITENFELD, Arch. f. Kinderh. **100**:155 (Sept. 29) 1933.

Encephalitis developed in a boy, 14 years old, nineteen days after the onset of chickenpox. There was bilateral choked disk of from 5.5 to 6 diopters caused by an obstructive hydrocephalus. Since lumbar puncture and aspiration of the ventricles did not relieve the intracranial pressure, the operation described by Foerster was done to provide a window in the corpus callosum for continuous drainage. Eight months later vision had become entirely normal. The rôle of allergy in the etiology of varicella encephalitis is discussed.

LEMASTER, Evanston, Ill.

CLINICAL CONTRIBUTIONS TO THE KNOWLEDGE OF GONORRHEA IN CHILDHOOD. PART V. L. V. DOBSZAY, Arch. f. Kinderh. **100**:210 (Oct.) 1933.

In the treatment of gonorrheal vulvovaginitis Dobszay uses vaginal tampons saturated with a solution of hydrochloric acid, pepsin and tannic acid. If the urethra and rectum are involved, the same solution is used by instillation. He has treated fifty-eight children by this method. The average time required for complete relief of symptoms was forty-eight days. Seventy per cent of the patients were shown to be permanently cured, as demonstrated by repeatedly negative results of provocative tests.

LEMASTER, Evanston, Ill.

AVERTIN AND THE SPECIFIC MANAGEMENT OF TETANUS. E. SEIFERT, Beitr. z. klin. Chir. **156**:1, 1932.

It is true that avertin does not work specifically on tetanus and is in the same category as morphine, magnesium sulphate, the sodium salt of secondary butyl beta bromallyl barbituric acid and chloral hydrate. But treatment with avertin is simple, sure and demonstrable. With the other drugs, such as morphine, large doses are necessary for effect. Seifert comes to the conclusion that tetanus antitoxin is effective only as a prophylactic and not as a cure.

RUBIN, Boston.

AN EARLY SIGN OF INFECTION WITH CHICKENPOX. O. LADE, München. med. Wchnschr. **80**:1215 (Aug. 4) 1933.

Lade has observed that many children have a diarrheal or very soft stool two weeks before the exanthem of chickenpox appears. In a ward in which the patients have been exposed to chickenpox each child who has a loose stool for no evident reason should be isolated. This observation also has a certain significance for the question of the portal of entry of the chickenpox virus. The author thinks that it indicates the intestinal route.

BRAHDY, Mount Vernon, N. Y.

PROPHYLAXIS IN MEASLES. F. HODER, München. med. Wchnschr. **80**:1286 (Aug. 18) 1933.

When convalescent serum is administered to a patient during the period of incubation of measles he may be protected entirely or he may have a modified form of the disease. If convalescent serum is not available, whole blood or serum from adults who had measles in childhood can be used with good results. Human serum is of no value once the clinical manifestations of the disease appear. The efficacy of animal serums has not been proved.

BRAHDY, Mount Vernon, N. Y.

TREATMENT OF POLIOMYELITIS WITH CONVALESCENT SERUM. H. HOEFFLER, München. med. Wchnschr. **80**:1367 (Sept. 1) 1933.

Hoeffler treated seven patients in the preparalytic stage of poliomyelitis with from 10 to 50 cc. of convalescent serum administered intramuscularly, and withheld the treatment from eight other patients who served as controls. Paralysis developed in two of the seven treated patients. One had a bilateral quadriceps paralysis, and the other, involvement of both upper extremities, but in each instance except for weakness in the deltoid muscles the paralysis disappeared within six weeks. Among the eight untreated patients extensive paralysis developed in one. Hoeffler also treated twenty-five patients in the paralytic stage with from 10 to 70 cc. of serum, and used sixteen untreated patients as controls. Four of the untreated patients died, whereas only one of the treated patients died. The paralysis seemed to improve or disappear more rapidly in the treated than in the untreated patients. He thinks that the serum may be even more effective, if given before meningeal irritation appears, when the patient has malaise, headache and pharyngitis. The difficulty of making a diagnosis is admitted. BRAHDY, Mount Vernon, N. Y.

CARDIAC CHANGES IN DIPHTHERIA. DONNERSTAG, Virchows Arch. f. path. Anat. **287**:421, 1932.

The municipal hospital of Stettin has experienced an increasing number of deaths from diphtheria during recent years. The author reports the significant finding in a series of the fatal cases. In most of them death occurred with symptoms of cardiac failure shortly after the onset of the disease. Though gross cardiac changes were rarely noted, microscopically some or all of the following alterations were demonstrated in all cases: diffuse or circumscribed fatty degeneration, myolysis or hyaline degeneration of the muscle fibers, interstitial inflammation and connective tissue proliferation. The latter two conditions were found only in the later stages of the disease. SAPHIR, Chicago. [ARCH. PATH.]

"SLOWLY DEVELOPING MENINGOCOCCUS SEPSIS" AND ITS TREATMENT WITH ACRIFLAVINE HYDROCHLORIDE. K. KASHIWABARA, J. Orient. Med. **19**:30 (Sept.) 1933.

In Dairen the author observed five patients with high, remittent fever, arthralgia and eruptions closely resembling erythema nodosum. It was thought that the condition resembled "slowly developing meningococcic sepsis" as described by Friedmann and Deicher, although meningococci could not be demonstrated in the blood. In each case the disease was immediately cured by injections of acriflavine hydrochloride.

LEMASTER, Evanston, Ill.

EXPERIMENTAL STUDIES OF POSTDIPHTHERITIC PARALYSIS. IV. HISTOLOGIC STUDIES ON THE CENTRAL NERVOUS SYSTEM IN A CASE OF POSTDIPHTHERITIC PARALYSIS. TSUNEHIKO MAKI, J. Orient. Med. **19**:34 (Sept.) 1933.

As a result of his experiments on rabbits Maki draws the conclusion that the endotoxin of diphtheria bacilli is the important factor in causing postdiphtheritic paralysis.

LEMASTER, Evanston, Ill.

PATHOLOGIC-ANATOMICAL AND BACTERIOLOGICAL STUDY ON HUMAN AND ANIMAL PERTUSSIS. SEIICHI INAMORI, J. Orient. Med. **19**:45 (Oct.) 1933.

The author has made histologic and bacteriologic studies of pertussis in human beings and the laboratory pertussis of the dog and monkey. In the laboratory pertussis there were no complications in the respiratory organs, in order to clarify the pathologic processes of pure pertussis. The observations are as follows:

1. The mucous membrane in one case of pertussis showed catarrhal inflammation extending from the larynx to the medium bronchus in the lungs. The larynx and the greater part of the trachea were involved especially for about the first two weeks after the outbreak of the disease, while the region from the lower part of the trachea down to the macrobronchus was most severely affected throughout the period of disease. The microbronchus and the pulmonary alveoli remained almost normal.

2. The lymph glands of both the trachea and the bronchus suffered from hypertrophy as early as the first week of the disease and remained unchanged until as late as the eighth or ninth week.

3. The outstanding feature of pure pertussis was the inflammation of the submucous and the surrounding tissues of the trachea, and especially of the bronchus, as well as of the interstitial tissue of the pulmonary alveoli. In the larynx and trachea the inflammation was alarming at the beginning, but moderated later. As the disease progressed the inflammation moved downward, involving the section below the ramification of the trachea, especially toward the microbronchus.

4. The inflammatory cells in the interstitial tissue at the beginning were the polymorphonuclear leukocytes, the large mononuclears and the eosinophils, but the polymorphonuclear cells later decreased in number; the large mononuclears thus dominated in number, with the lymphocytes making a late appearance, followed finally by the connective tissue cells.

5. The sections of the wall of the respiratory tract which were infected by pertussis bacilli in cases of pure pertussis were, in the early stages, the mucous membrane of the macrobronchus and its upper region. Inside the lungs the bacilli decreased in number toward the lower sections. Only a few were found in the medium bronchus and microbronchus, and in the pulmonary alveoli their presence could be attested only with difficulty.

6. Observation of the sections of the submucous and surounding tissues of the respiratory tract infected by pertussis bacilli in cases of pure pertussis revealed that during the first week of the disease the whole area of the respiratory organ, that is below the larynx down to the microbronchus, was affected. As the pertussis progressed the bacilli first decreased in the upper region of the tract, whereas they increased in the region below the ramification of the trachea during the second week. At the macrobronchus and medium bronchus the number of bacilli was greatest between the third and the fifth weeks, after which they began to decrease gradually. This shift of local distribution of the pertussis bacilli in conjunction with the progress of the disease coincides histologically with the peribronchitis which invades the peripheral region more severely as the disease progresses and stubbornly persists there for some time.

7. With reference to the course of the shift of the pertussis bacilli in the respiratory organ, it is safe to assert that the bacilli invade the respiratory tract as far down as the macrobronchus, which connects with the trachea at the ramified section, whereupon they invade the submucous tissue and spread into the surrounding tissue. While in this tissue they shift their course retrogressing against the lymphatic stream into the peripheral region, finally reaching the interstitial tissue of the pulmonary alveoli.

8. The excretion, by way of the blood stream, of the endotoxin of the pertussis bacilli and the invasion of the tissues by the bacilli themselves are both causes of peribronchitis, which is one of the characteristic features of pertussis.

9. Pertussis bacilli may cause simple interstitial inflammation, but they never seem to bring forth parenchymatous pneumonia. Interstitial inflammation, however, paves the way for secondary deep infection by miscellaneous bacilli, in consequence of which such a special change as pertussis-pneumonia is caused. It appears to be at this stage that the pertussis bacilli extend their invasion into the microbronchus and the pulmonary alveoli.

10. With regard to the length of time pertussis bacilli can stay alive in the respiratory organs (of monkeys, for example), the possible maximum is about six weeks in case of pure pertussis and more than ten weeks in case of complication with catarrhal pneumonia.

AUTHOR'S SUMMARY.

HERPES ZOSTER AND CHICKENPOX. CURT GYLLENSWÄRD, Acta pædiat. **14**:584 (July 12) 1933.

The author adds to the already long list two more separate instances in which herpes zoster in one patient was followed after a suitable period of incubation by varicella in other susceptible persons, without discoverable exposure of the latter to other sources of chickenpox.

McCUNE, New York.

LEUKOCYTE COUNTS IN MEASLES. H. BJÖRN-HANSEN, Acta pædiat. (supp. 1) **14**:1, 1932.

The number of patients studied by the author was small, but the intensiveness of the investigation as regards the hematologic changes in measles is unique. For this reason the article, which is quite long, does not lend itself well to condensation; its chief value lies in the detailed presentation of repeated careful blood counts.

Twelve patients with measles were studied daily from early in the course—generally before the appearance of Koplik's spots—well into convalescence, and for each case there are presented both in graphs and tables the observations of temperature, the total leukocyte count, the differential count and the Schilling partition of neutrophils, together with essential clinical data. In ten additional cases the study was undertaken at the height of the disease. During the period of incubation, up to a week before the appearance of the eruption moderate leukocytosis may be found. With the outbreak of symptoms there occurs a fall in the total leukocyte count, caused chiefly by a decrease in neutrophils but comprising also a lowering of the absolute number of lymphocytes; the Schilling count shows a marked shift to the left, and immature lymphocytes and degenerative forms appear. These changes occur independently of the coincident appearance of septic complications; in other words, the development of otitis or pneumonia at the height of the disease fails to effect leukocytosis, as it would be expected to do in the absence of measles. With recovery, the blood picture returns to normal in the course of a few days.

The leukocytosis of the period of incubation is interpreted as the result of the stimulation of bone marrow. By analogy, the leukopenia found at the height of the disease would appear to denote a paralysis of the function of the bone marrow as concerns the liberation of granulocytes. This interpretation is confirmed by applying stimulus (intramuscular injection of sterile milk) to the bone marrow of patients with measles at the height of the disease, at a time when leukopenia prevails. Control studies were made on normal subjects who had been given injections of milk to establish the expected reaction in the circulating blood: an increase of over 100 per cent in the total leukocyte count, brought about entirely by the increase in neutrophils, with a normal proportion of mature and immature

forms. Patients studied at the height of the disease failed to show a significant leukocyte response to injections of milk with but one exception. These results suggest that the bone marrow is exhausted or, at least, refractory during the course of uncomplicated measles. In fact, by direct comparison, the response of the bone marrow during measles is shown to be analogous to that in patients with sepsis, in whom the bone marrow likewise proves to be refractory to stimulation by injections of milk.

Ehrlich's diazo reaction in the urine, which is almost constantly positive in measles during the eruptive stage, is causally linked with the lymphopenia as an expression of overactive destruction of tissue cells, particularly of lymphocytes. This portion of the work is not fully convincing to the reviewer.

Two cases of rubeola, in which similar intensive studies of the blood were carried out, are reported.

Students of measles, particularly of its effect on the morphologic elements of the blood, will find this a most valuable article.

McIntosh, New York.

Schultz-Charlton Blanching Phenomenon in Scarlet Fever. R. Huss, Acta pædiat. (supp. 3) **14**:1, 1933.

In this monograph of about 150 pages a critical summary of all the published work pertaining to the Schultz-Charlton phenomenon is presented, as well as new clinical and experimental data from the Stockholm municipal hospital for infectious diseases. The new material on this subject is virtually as extensive as all previously published series taken together.

Other authors have generally had better success in evoking the blanching phenomenon with the use of specific antiserums than with convalescent serums. Huss obtained a positive blanching reaction with antiserum in 60 per cent of a group of patients with scarlet fever eruptions and with convalescent serum in 86 per cent. The blanch test is more readily obtained in relapsing scarlet fever than with a first eruption. In second attacks, of which 35 cases are reported, the blanch test is produced about as frequently as in first attacks. Data are given regarding the blanch test in special forms of scarlet fever — surgical, puerperal, traumatic and the type associated with burns. Other forms of blanching are discussed: blanching with normal human serums, with nonspecific horse serums and other serums, with epinephrine or calcium solutions and blanching in eruptions other than scarlatinal.

Under certain conditions the scarlatinal eruption will spare a given area of the skin at the site of injection of vaccine or serum, in the neighborhood of a preexisting dermal lesion of infectious or other nature and, under certain circumstances, at the site of a previously placed Dick test. These are all discussed under the category of the pseudoblanching phenomenon. It is shown that blanching is most successful on the first or second day of the eruption; thereafter it becomes progressively less reliable.

At the time when a successful blanch test is made the results of the Dick test in the patient may be either positive or negative. Serum from a donor in whom the Dick test has given negative results nearly always has blanching power; serum from donors in whom the Dick test has given positive results has blanching power in about half the cases. During the first three or four days of the eruption the patient's own serum is without blanching power when tested on his own or another patient's eruption, but during a relapse it is possible for the patient's own serum to blanch his eruption, though this is exceptional. It is even possible for a patient's serum to have blanching properties prior to classic scarlet fever. To a certain extent, the absence of blanching power in the presence of a scarlatiniform eruption which has been present for not more than three days is a feature of diagnostic significance. The limitation of its usefulness is the requirement that

a second patient with indubitable and early scarlet fever be available for the making of the test.

In the second half of the work, which is devoted to an investigation of the mechanism of the blanching phenomenon and of the nature of Dick "toxin," experiments are described in which various mixtures of blanching serum and scarlatinal streptococcus toxin were injected into an area covered by the eruption and into another area free from eruption; the injections were made simultaneously and into the same patient. From these it is concluded that the substance which is responsible for blanching and the substance which is capable of neutralizing the toxin are separate and distinct. In all probability, blanching is brought about by an antitoxin; but the corresponding antigen is not limited to a specific strain of streptococcus; it is also found to a less extent in many strains of streptococcus and probably in other organisms as well (e. g., staphylococci).

Dick "toxin," which was at first thought to be a toxin of the classic type, was shown in earlier investigations to act by a mechanism comparable in many respects to anaphylaxis or sensitization; it was demonstrated that its toxic properties were secondarily acquired, depending on previous sensitization either by bacterial invasion or by artificial inoculation. After sensitizing guinea-pigs with injections of Dick toxin, the author attempted to demonstrate the presence of an allergen by subsequently inducing the classic anaphylactic response with an intravenous injection of the shocking dose of the same material. The only allergen that could be demonstrated in ordinary Dick toxin was that which is inherent in the culture mediums generally employed; toxin produced by growth of the organisms on a special medium which was incapable of evoking by itself an anaphylactic response proved to be free from sensitizing properties. The allergen present in Dick toxin was shown to be thermolabile; it was destroyed by heating in a water bath at 100 C. for an hour.

Further experiments are reported in which the author strove to determine whether the Dick toxin was neurotropic. The evidence was either negative or equivocal. In the discussion of this aspect, all the evidence which supports the concept that the Dick filtrate is a true toxin is arrayed against that which would favor the hypothesis of an allergen. An unqualified answer is not permissible.

An excellent bibliography is appended.

McINTOSH, New York.

THE ELECTROCARDIOGRAM IN SCARLET FEVER. J. WICKSTRÖM, Acta pædiat. (supp. 4) **14**:1, 1933.

This is the record of an intensive study of 100 cases of scarlet fever, in which 2,669 electrocardiograms were made, an average of 1 for every two and five-hundredths days of illness in each case. Many of the patients were followed for several months. Of the series, 84 patients were less than 15 years of age; 13 showed a relapse. In a control series of 10 normal persons, 98 electrocardiograms were made.

Thirty-five per cent of the group showed a prolongation of the P R interval amounting to from 0.01 to 0.04 second during the acute stage of the disease; in 32 per cent there was prolonged conduction time at some later period, but the prolongation was still referable to the disease. In 25 per cent there was prolongation of the Q R S interval, and in 46 per cent there was abnormal rotation of the electrical axis of the heart. A considerable proportion showed also a change in the T wave in lead I or II. Myocardial damage was shown in 86 per cent. These were mainly "inhibitory effects" and are comparable to those found in patients with rheumatic fever, though they are of less pertinacity. Irritative phenomena, such as extrasystoles and shift of the pacemaker, were rare.

Electrocardiographic changes were more common in patients who presented clinical toxic symptoms, who had a high temperature and who showed urobilinemia. There was no special correlation between the presence of electrocardiographic changes and the type and frequency of complications. Strangely enough, there was also no correlation with the usual purely clinical criteria of cardiac involve-

ment, as shown by physical signs. Young patients appeared to be relatively free from electrocardiographic changes in scarlet fever. Patients with a previous history of infectious disease of any kind were three times as prone to show electrocardiographic changes as those who had had no such illness.

The prognosis of these changes is good. In 40 per cent of the cases studied they disappeared before the patient left the hospital; in 38 per cent they disappeared within an average observation period of five and a half months; in the remainder they still persisted after an average follow-up period of seven and a half months. Serum therapy appeared to have no influence on their occurrence or persistence.

Case reports occupy 52 pages; discussion of material, 91, and a bibliography, 6.

McIntosh, New York.

Chronic Infections

Pulmonary Tuberculosis in Childhood. Bruce Chown and Harry Medovy, Canad. M. A. J. **29**:364 (Oct.) 1933.

Tuberculosis of the lung is a common disease of childhood, and pursues a benign course provided the infecting source is removed early. Every time an adult is discovered with tuberculosis all children with whom he has been in contact are suspect, and, vice versa, the finding of a tuberculous infection in a child should lead to a search for the source among its adult associates. Early breaking of contact is the one great life-saving measure for a child. The authors emphasize the paucity of physical signs and the importance of taking a careful history and making tuberculin tests in diagnosis of tuberculosis. Every child who reacts to tuberculin should have a roentgen examination of the chest, and his associates should be most carefully passed under review. Brief descriptions of the pathologic and roentgen findings are given.

Moore, Omaha.

Tissue Culture Studies on the Relation of the Tuberculin Reaction to Anaphylaxis and the Arthus Phenomenon. J. D. Aronson, J. Immunol. **25**:1 (July) 1933.

The effect of the addition of antigen to cells taken from sensitized and non-sensitized guinea-pigs and maintained by tissue culture was studied. Explants from the spleen and bone marrow were used. It was found that the growth and migration of cells of a tuberculous animal were inhibited by the addition of tuberculin to the culture. There was no inhibition of the growth of cells of a normal guinea-pig previously sensitized to horse serum on the addition of horse serum to the culture. Similarly, there was no inhibition in explants of a tuberculous animal sensitized to horse serum when the latter was added to the culture. Tissue cultures from normal and tuberculous animals in which the phenomenon of Arthus had been elicited were unaffected by injections of horse serum. Aronson suggests that the mechanism underlying the tuberculin reaction is different from the mechanism of anaphylaxis and from that of the phenomenon of Arthus.

Fothergill, Boston.

Complement-Fixation with S and R Antigens and the Sera of 100 Cases of Tuberculosis. C. E. Rice, J. H. Orr and G. B. Reed, J. Immunol. **25**:19 (July) 1933.

Smooth and rough cultures of tubercle bacilli were employed as antigens in a study of complement fixation in patients with tuberculosis in various stages of activity. The two antigens worked equally well in detecting complement-fixing antibodies in the serums of patients with tuberculosis of the chronic type. In the majority of cases of the acute type the S antigen fixed about twice as much complement as the R antigen. The authors suggest that, while their data are insufficient to establish it, the "S to R antibody index" may prove of value in prognosis.

Fothergill, Boston.

IMMUNIZATION PHENOMENA IN RABBITS VACCINATED WITH HEAT-KILLED TUBERCLE BACILLI. A STUDY OF THE CUTANEOUS REACTIONS AND THE DEVELOPMENT OF BACTERIOTROPINS. J. HUGHES, J. Immunol. **25**:103 (July) 1933.

Hughes found that the serum of rabbits immunized with heat-killed tubercle bacilli showed a progressive increase in its ability to promote phagocytosis by both polymorphonuclear and mononuclear leukocytes. These two types of cells paralleled each other in activity during the development of bacteriotropic action. Infection with living organisms stimulated an earlier development of bacteriotropic action than did repeated injections of organisms killed by heat. Bacteriotropic activity appeared earlier than sensitivity, as indicated by the cutaneous reaction to injection of dead tubercle bacilli.

FOTHERGILL, Boston.

THE TUBERCULIN SKIN TEST. HILLA SHERIFF, J. South Carolina M. A. **29**:253 (Nov.) 1933.

The Mantoux or intracutaneous test is preferred to the von Pirquet and other methods of testing for tuberculosis. It can be administered quantitatively, with accurate control. If one reading is to be had, the most desirable time is at the end of seventy-two hours. The tuberculin test should be more widely used, especially in infants and young children, since it is in these that more can be done, if there is any suspicion of tuberculosis. Sheriff recommends that all patients coming from tuberculous homes be tested with the Mantoux test, the test to be repeated, if negative, in six months. If the tuberculin test is used as a routine, the greater number of suspects will be found and earlier diagnosis will be made, which will lead to the proper treatment of the tuberculous patient and protection for others.

WESTON, JR., Columbia, S. C.

HUMAN AND BOVINE INFECTION IN EXTRAPULMONARY TUBERCULOSIS. C. S. CHANG, New England J. Med. **209**:690 (Oct. 5) 1933.

The paper concerns patients with extrapulmonary tuberculosis at the Lakeville State Sanatorium, and the object is to present the percentages infected with human and bovine tubercle bacilli respectively. The method of procedure was as follows: 1. From each patient a sample of pus or of broken-down tissue or a specimen such as a gland was obtained, and the material emulsified and injected into guinea-pigs. Only the patients shown to have tuberculosis at autopsy of the guinea-pigs were studied. 2. When a guinea-pig showed tuberculosis, tubercles were taken from its spleen and cultures were made. Smith's acid reaction test was then performed and rabbits were inoculated with the bacilli. 3. The result was, first, a positive bacteriologic proof that the lesion in question was tuberculosis and, second, information as to whether the infection was with bovine or with human tubercle bacilli.

Tuberculosis of the hip predominated in frequency in both the adults and the children, making up 45, or 24 per cent, of the 200 cases. Tuberculosis of the spine was next in frequency, with 28 cases, or 14 per cent; tuberculosis of the glands ranked next with 21 cases, or nearly 10 per cent.

Of the 200 patients studied, 145, or 72.5 per cent, were infected with human tubercle bacilli, and 55, or 27.5 per cent were infected with bovine tubercle bacilli. Children under 5 years of age, however, showed 71 per cent infections with bovine tubercle bacilli, whereas those over 17 years of age showed only 11 per cent. Universal tuberculin-testing of herds and universal pasteurization of milk seem justified, as most of the cases came from communities in which neither was being done.

GENGENBACH, Denver.

A RÉSUMÉ OF THE STUDY OF CHILDHOOD TUBERCULOSIS IN TEXAS. ELVA A. WRIGHT, Texas State J. Med. **29**:426 (Nov.) 1933.

This paper is a statistical report of the activities of the organizations concerned with tuberculosis in Texas during the past two years. The Committee on Standardization of the Tuberculin Skin Test, appointed by the Texas Tuberculosis Association, recommended that the plan outlined by the Massachusetts Department of Health be adopted. A committee of the Texas Tuberculosis Association has outlined "A Five Year Plan for the Study and Control of Childhood Tuberculosis." A uniform examination blank was created by a committee of the Texas Tuberculosis Association, to be used in the general examination of all school children. Last year some twenty-five thousand children were studied in Texas, and it is believed that the time will soon come when every school child in the state will be given the tuberculin skin test for tuberculosis. The Antituberculosis League of Houston made a survey of nine city and thirty-one county schools in 1932. It is hoped that at least fifty thousand tests will be made throughout the state in 1933. The cost of the testing for 1932 was: solution, $26.00; instruments, $9.00; needles, $6.30; alcohol and cotton, $3.96, making a total of $45.26.

In Abilene it was considered more practicable and much less expensive to give the tuberculin test to all new high school students, rather than to give a complete physical examination to all high school students. Of those students tested who gave positive reactions and who were also underweight or who had questionable symptoms, some were selected for roentgen examination. A number of these were then referred to their family physicians for further examination. The author is convinced that the fight against tuberculosis is narrowing down to the study of the disease in young children, and quotes at length the literature of the National Tuberculosis Association, which is of the same opinion.

MOORE, Dallas, Texas.

CHILDHOOD TUBERCULOSIS: ITS PREVALENCE AND INFECTIVITY IN A SOUTH-WESTERN COMMUNITY (A PRELIMINARY REPORT). JOHN G. YOUNG, Texas State J. Med. **29**:429 (Nov.) 1933.

For this study 14,358 children from 2 weeks to 14 years of age were examined in a clinic. The aim was to determine the incidence of tuberculous infection and to determine the presence of disease in those infected. Mantoux tests were done, with many retests; roentgen examinations were made of all those with a positive reaction, temperature charts were studied, the examinations were repeated and in some cases an attempt was made to recover the tubercle bacillus.

Seventeen and seven-tenths per cent of the children exhibited a positive reaction to the intradermal tuberculin test. Of this group, many more showed a positive reaction to the 1:100 dilution than to the 1:1,000 dilution. When there were good reasons to believe that a tuberculous infection was present, there was no hesitancy in using a 1:10 dilution, and thus a positive reaction was revealed in some children who otherwise would have given a negative reaction. No serious reaction occurred, though some children had a large local reaction and fever for two or three days.

With regard to the infected ones a diagnosis of tuberculous disease was made in 29 per cent of those with a positive reaction; the younger the children the greater the percentage, this being 100 in early infancy.

With regard to the diagnostic criteria, by far the most important were the results of the Mantoux tests and roentgen examinations of the chest.

In determining the infectivity of these rather active, apparently well children, an attempt was made to ascertain whether any were giving off tubercle bacilli. The group in whom tuberculosis had been diagnosed were submitted to gastric lavage, cultures were made and guinea-pigs inoculated. A surprising percentage

showed the organisms in active, virulent form—30 per cent. The danger of contact with these children must be recognized; it is a problem that faces the medical profession and co-workers of the general public, especially the social worker.

MOORE, Dallas, Texas.

GENERAL LIGHT BATHS IN SURGICAL TUBERCULOSIS. HENRY GAUVAIN, Brit. J. Phys. Med. **8**:19 (June) 1933.

Gauvain stresses the importance of treatment by sunlight over treatment by artificial light. He thinks that alternations of light and shade, of heat and cold and of humid and dry air are of great importance in the treatment of surgical tuberculosis.

HARTMAN, Cleveland.

DIAGNOSIS AND TREATMENT OF SECONDARY INTESTINAL TUBERCULOSIS. LAWRENCE BROWN and HOMER L. SAMPSON, Brit. J. Phys. Med. **8**:58 (Aug.) 1933.

The authors describe in detail roentgenologic methods for the diagnosis of tuberculous enteritis and colitis. The former is said to be much more difficult to diagnose than the latter. In a series of autopsies in which intestinal tuberculous ulceration was found, the iliocecum or ascending colon was involved in over 95 per cent of the cases.

The authors treated their patients with artificial light. They do not believe that hemoptysis and high fever are contraindications to the use of this therapy. The results of the treatment were studied by observation of symptoms, by roentgen examinations, by autopsies and by the application of statistical methods having in view the length of life and the number "living" and "dead." The authors believe that light therapy has a definite place in the treatment of intestinal tuberculosis.

HARTMAN, Cleveland.

CLINICAL MANIFESTATIONS OF PULMONARY TUBERCULOSIS IN CHILDHOOD. W. BURTON WOOD, Lancet **2**:797 (Oct. 7) 1933.

"Phthisis is one of the rarest of the diseases of childhood, and as it is improbable that the disease was ever common in the early years of life it is not very easy to understand the fear of consumption in childhood, which still prevails among the laity and even to some extent in the profession."

In diagnosis we must depend almost entirely on roentgenograms of the chest. Excluding those cases in which roentgen examination reveals calcified foci in the lung fields and calcified nodes at the lung roots, Wood recognizes six varieties of pulmonary tuberculosis. In the benign group he lists: (1) tuberculous adenitis and "epituberculous" manifestations; (2) chronic miliary tuberculosis; (3) tuberculous pleurisy with effusion. In the serious group he places: (1) acute miliary tuberculosis; (2) tuberculous pneumonia; (3) the adult type of phthisis.

In regard to epituberculosis, it is stated that the results of the few postmortem examinations that have been made are conflicting and that it would be wiser to suspend judgment until further evidence is forthcoming. It is evident that some cases resembling epituberculosis are due to atelectasis, and it is probable that other factors are at work in other cases.

LANGMANN, New York.

PRACTICAL APPLICATION OF CULTURES ON LOEWENSTEIN'S MEDIUM IN THE DIAGNOSIS OF TUBERCULOUS MENINGITIS. H. GRENET and P. ISAAC-GEORGES, Bull. Soc. de pédiat. de Paris **30**:498 (Oct. 18) 1932.

Cultures on Loewenstein's medium were made from the spinal fluids obtained from ten patients with tuberculous meningitis. They all yielded macroscopic colonies of B. tuberculosis in from thirteen to forty-five days. Microscopic examination of scrapings from the surfaces of the cultures showed tubercle bacilli in

five, six and seven days, respectively, after three of the cultures were planted, and in most of the cases they were demonstrated microscopically before the end of the third week of growth of the cultures. This method also has the advantage that it furnishes the bacteriologist with cultures of the etiologic organism, which may open the road to important research.

BENJAMIN, Montreal, Canada.

CONGENITAL SYPHILIS. J. CATHALA, Paris méd. **2**:329 (Oct. 28) 1933.

Cathala makes an extensive but interesting résumé of the entire subject. In France the frequency varies from 2 per cent, reported by Nassau, to 25 per cent, reported by Marfan in the Enfants-Assistés. In the new-born, besides the usual signs, attention is drawn to the osteochondritis of Wegner, the habitual vomiting of Marfan and the isolated convulsions, also described by Marfan. In older children all obscure anemias or dystrophies should arouse suspicion. Treatment should be given in all cases of doubt.

SANFORD, Chicago.

GENERAL PRINCIPLES OF PROPHYLAXIS AGAINST TUBERCULOSIS IN THE INFANT. LÉON BERNARD, Rev. franç. de puériculture **1**:65 (May) 1933.

Prophylaxis of tuberculosis in the infant may be accomplished by education and supervision of the tuberculous patient in the household or by removal of the child from the tuberculous home. The organization founded by Grancher takes children between the ages of 3 and 13 from households in which there is tuberculosis and places them in good country homes. Bernard has applied the same method with small infants who have not been infected, with the additional precaution that they are placed only in homes in which constant supervision by a physician and a visiting nurse is possible. Infants and children already giving a positive tuberculin reaction, but with no clinical symptoms, are placed in a preventorium for observation before being sent to private homes. A third method of prophylaxis, the use of B C G vaccine, has been proved harmless and of a certain efficacy. Children vaccinated with B C G should not return to the tuberculous household until immunity has had time to develop. It is the dispensary, with its medicosocial organization, which is the basis of all prophylaxis against tuberculosis.

CRANE, Chicago.

ORGANIZATION OF THE CAMPAIGN AGAINST THE PERIL OF SYPHILIS. CAVAILLON, Rev. franç. de puériculture **1**:129 (June) 1933.

A law has been presented to the French parliament which is designed to create a department to combat venereal disease with a more solid organization than that now existing; because of the varying needs of the different sections of the country local organizations are not limited to any one type. In the cities, large dispensaries for diagnosis and treatment of syphilis should be conveniently located and equipped to give prompt service so as not to discourage the return of the patient for regular treatment. In small communities clinics for venereal disease can be satisfactorily combined with the clinics for tuberculosis. The social worker has a most important part in the campaign in the education of the patient, assuring regularity of treatment, aiding in the discovery of the source of infection, bringing for examination persons who may have been contaminated and bringing necessary relief to the patients or their families.

CRANE, Chicago.

HEMATOCYTOMETRIC AND MORPHOLOGIC STUDIES AND THE SCHEME OF ARNETH IN CONGENITALLY SYPHILITIC INFANTS. GIOACCHINO STANCANELLI, Pediatria **41**:1 (Jan.) 1933.

Based on the results of studies of the blood of thirty-four children with congenital syphilis varying in ages from a few months to 9 years, the author concludes that the blood picture, though constantly altered in various degrees, does

not furnish decisive data for diagnosis. These hematologic alterations, however, especially in conjunction with the neutrophilic picture of Arneth, offer great possibilities for evaluating the degree of pathogenesis resulting in the hematopoietic tissues and through this the possibility of important prognostic deductions.

SIGNORELLI, New Orleans.

FACTORS DETERMINING THE RARITY OF LARYNGEAL TUBERCULOSIS IN INFANCY. ESPEDITO DI LAURO, Pediatria **41**:62 (Jan.) 1933.

The author's conclusion is that the rarity of laryngeal tuberculosis during infancy is directly due to the lymphatic constitution and the construction of the larynx during infancy.

SIGNORELLI, New Orleans.

A CONTRIBUTION TO THE STUDY OF TUBERCULOUS BACILLEMIA IN INFANCY. A. LAURINSICH and E. ZAMBRANO, Pediatria **41**:1225 (Oct. 1) 1933.

A series of investigations were undertaken with a view of checking the work of Löwenstein and his co-workers. After giving a detailed account of their own technic and observations, the authors conclude that their results do not permit them to subscribe to the conclusions arrived at by Löwenstein and his co-workers. Therefore, they believe that the work of Löwenstein does not modify the conception previously acquired in relation to tuberculosis, bacillemia, pathogenesis and diagnosis.

SIGNORELLI, New Orleans.

PRIMARY GLANDULAR-PULMONARY TUBERCULOSIS IN INFANCY. E. SCHWARZ, Pediatria **41**:1249 (Oct. 1) 1933.

Schwarz gives a detailed discussion of tracheobronchial adenopathy in general, based on recent beliefs and personal observation. He attempts to fix definite limits in the clinical picture of these lesions in infancy. He has examined minutely the various clinical and radiologic manifestations which can be ascribed to the various phases of tuberculosis, pointing out the necessary difficulties inherent in anatomic causes, as well as the topographic relationship, with special regard to possible errors of interpretation of mediastinal shadows. These difficulties assume increased proportions during early infancy as the glandular lesion assumes dimensions greatly out of proportion. He concludes that the definite diagnosis of glandular alterations is very difficult, but that this diagnosis can be arrived at indirectly by basing it on ascertainable symptoms of coexisting pulmonary lesions.

SIGNORELLI, New Orleans.

DIAGNOSTIC VALUE OF THE SERUM REACTION OF LEUCHTENBERG AND LORENZ IN TUBERCULOSIS OF CHILDHOOD. L. CERZA, Pediatria **41**:1337 (Nov.) 1933.

Cerza studied the diagnostic value of the serum reaction of Leuchtenberg and Lorenz in 105 children suffering from various forms of tuberculosis, including the latent form. The study was controlled by observations on patients suffering from diseases other than tuberculosis. In 51 cases the results were constantly positive, in accordance with the positive findings of cutaneous and intradermal tests. In 44 cases of nontuberculous conditions there were six positive reactions in children who had congenital syphilis. A marked sensibility to the human tuberculous antigen was constantly observed. Cerza directs attention to the positive results of these reactions, based on a nonspecificity in 13.6 per cent. Of greater importance was the behavior of the reaction in children apparently normal, who were exposed to massive contagion and treated with the antituberculous vaccine of Maragliano. In these cases the reaction demonstrated a greater usefulness than the cutaneous or intradermal tests, from the standpoint of both sensitiveness and early appearance of the positive results.

This leads him to contend that the reaction, especially with improved technic could possibly contribute to a better recognition of the allergic state of tuberculosis.

SIGNORELLI, New Orleans.

SEROLOGY IN TUBERCULOSIS IN CHILDREN. H. BISCHOFF and H. NAGELL, Arch. f. Kinderh. **101**:74 (Jan. 31) 1934.

The complement-fixation test for tuberculosis, with the Witebsky antigen, was performed on 125 children. Of 12 patients with florid tuberculosis, only 2 responded with positive reactions. There was one positive reaction in 13 cases of inactive tuberculosis and one positive result in 100 children who were clinically free from tuberculosis. The conclusion is either that children do not produce antibodies in response to a tuberculous infection or that the technic of the complement-fixation test for tuberculosis is unsatisfactory.

LEMASTER, Evanston, Ill.

ERYTHEMA NODOSUM AND SUBSEQUENT TUBERCULOSIS. H. J. USTVEDT and A. S. JOHANNESSEN, Acta med. Scandinav. **80**:262 (Sept. 29) 1933.

The study is based on the follow-up of 314 patients treated for erythema nodosum in Oslo between 1916 and 1932. Ninety-two and three-tenths per cent of these had been followed satisfactorily.

Only 9 per cent of the patients were male. The predominance of females was not so marked in the group under the age of 15 years, in which there were 22 girls and 13 boys. The seasonal and the age incidence of erythema nodosum coincide with those of pulmonary tuberculosis in Norway.

Of the persons who contracted erythema nodosum, 10 per cent manifested signs of tuberculosis during the first year, 3 per cent in the second and third year, and 1 per cent in the fourth and fifth year; only one showed such signs beyond the fifth year. In this they were in contrast to the patients with "primary pleurisy" who, though manifesting tuberculosis in the same percentage in the first year, later had a much higher morbidity and mortality extending over the whole ten year period of the study. Ten per cent of the patients had recurrences with a sudden progression of the tuberculous process.

Ustvedt and Johannessen believe that erythema nodosum is an allergic manifestation of tuberculosis.

KAJDI, Baltimore.

INTESTINAL TUBERCULOSIS. H. Vos, Nederl. tijdschr. v. geneesk. **77**:5181 (Nov. 18) 1933.

Intestinal tuberculosis is a common complication of pulmonary tuberculosis. The diagnosis is to be made essentially by means of roentgen examination, which may reveal slight signs in many cases. The classic diarrhea is in most cases a terminal phenomenon. The prognosis of intestinal tuberculosis is generally not unfavorable, and if the diagnosis is made in time, depends principally on the severity of the pulmonary disease. The treatment, consisting of a diet rich in vitamins (cod liver oil with tomatoes or oranges), in many cases combined with heliotherapy, often gives excellent results. Some observations are reported.

VAN CREVELD, Amsterdam, The Netherlands.

Internal Diseases

A PRELIMINARY REPORT ON THE CURE OF NUTRITIONAL ANEMIA BY ONE OF THE LEGUMES. D. H. COOK and TRINITA RIVERA, Am. J. Trop. Med. **13**:327 (May) 1933.

The authors review briefly the treatment of anemias and report their results of the treatment of nutritional anemia with one of the legumes (Gandul).

They produced anemia in rats aged 4 weeks, by feeding them on a dry Klim diet. When the animals were sufficiently anemic (the hemoglobin varying from

25 to 30 per cent), they were divided into groups and fed on varying amounts of fresh gandules or the ash from the same amount of fresh gandules and Klim. The animals were kept on their respective diets for five weeks, during which time weekly determinations of hemoglobin, the gain or loss in weight and the amount of food consumed were made.

The authors conclude that gandules or pigeon peas exhibited curative properties in nutritional anemias, and that the fresh peas showed greater regeneration than the ash of equivalent quantities when both were fed at levels suboptimal for normal regeneration of hemoglobin.

BURPEE, Augusta, Ga.

ENDOCRINE GROWTH DEFICIENCIES: DIAGNOSIS AND TREATMENT; A PRELIMINARY CLINICAL REPORT. WILLIAM ENGELBACH, R. L. SCHAEFER and W. L. BROSIUS, Endocrinology **17**:250 (May-June) 1933.

The authors report the cases of seven children with marked deficiency of growth in whom extrinsic factors were eliminated. All were treated by injections of a specific growth hormone isolated from the anterior lobe of the pituitary gland.

These cases all fell into group 1 of the following suggested classification of endocrine growth deficiencies:

1. Aneoplastic (functional) deficiencies:
   - (*A*) Hypopituitarism (anterior lobe deficiency)
   - (*B*) Hypopituitarothyroidism (primary deficiency of the anterior lobe of the pituitary gland and secondary thyroid deficiency)
   - (*C*) Hypothyropituitarism (primary thyroid deficiency and secondary deficiency of the anterior lobe of the pituitary gland).
2. Neoplastic deficiencies (intrasellar and extrasellar tumors).
3. Hypergenitalism, parathyroidism and suprarenalism.

These seven children, who presented various degrees of dwarfism, all showed a favorable response to treatment with an anterior lobe pituitary preparation. During treatment with the growth hormone their height increased from 1 to 2 7/10 inches (2.5 to 6.75 cm.) during periods of from three to five months, as contrasted with practically no growth during control periods. One child grew ½ inch (1.27 cm.) in five months under thyroid therapy, and when placed under treatment with an anterior lobe pituitary preparation he grew 2 7/10 inches (6.75 cm.) in five months.

This report indicates that the growth hormone is a specific stimulant of growth in the human being.

JACOBSEN, Buffalo.

DISEASES OF THE SUPRARENAL GLANDS. LEONARD G. ROWNTREE and RALPH G. BALL, Endocrinology **17**:263 (May-June) 1933.

After a brief review of the experimental work which led to the discovery of the suprarenal cortical hormone and a discussion of the relation of the suprarenal gland to other glands of internal secretion, a classification of diseases of the gland is presented:

Hyperfunction:

Cortical (*syndrome genitosurrénale*), gives rise to:

1. Congenital pseudohermaphroditism
2. Infantile pubertas praecox
3. Adult virilism and hirsutism

Medullary, may be associated with:

1. Neuroblastoma with multiple metastases to the liver and bones
2. Benign ganglioneuroma
3. Paraganglioma with intermittent paroxysmal hypertension or permanent hypertension

Hypofunction:

Suprarenal insufficiency (hyposuprarenalism)

Addison's disease

A case of precocious sexual development in a girl aged 4 years is presented; however, a positive diagnosis of suprarenal dysfunction was not considered justifiable. A second similar case in a boy, aged 30 months, with a low-pitched masculine voice, profuse pubic hair and large external genitals is reported. There was a large abdominal tumor, and the diagnosis of suprarenal tumor was suggested but could not be verified.

Cases of medullary hyperfunction are due to tumors of the following varieties:

1. Neuroblastoma, of which there are three clinical types characterized by: (*a*) metastasis to the liver and the lungs or to the abdominal lymph nodes (Pepper's type); (*b*) metastatic involvement of the orbit, the skull and the long bones (Hutchinson's type); (*c*) severe anemia suggesting the pernicious type (Goldzieber's type).

2. Ganglioneuroma, which is rare, usually being found incidentally at necropsy (metastasis is rare).

3. Paraganglioma, which may cause intermittent hypertension on continuous hypertension, sometimes with diabetes.

The cases of seven children who had tumors of the Hutchinson type are recorded; one came to autopsy. The remainder of the paper is concerned chiefly with adult types of disturbances of the suprarenal glands.

JACOBSEN, Buffalo.

THE TREATMENT OF AGRANULOCYTOSIS WITH ADENINE SULPHATE. PAUL REZNIKOFF, J. Clin. Investigation **12**:45 (Jan.) 1933.

In eleven of fifteen uncomplicated cases of agranulocytosis, treatment with adenine sulphate was followed by recovery. In severely complicated cases this therapy was not effective.

The dosage used for adults was 1 Gm. of adenine sulphate boiled in from 35 to 40 cc. of physiologic solution of sodium chloride, sufficiently warm to prevent precipitation, administered intravenously three times a day for at least three days. As much as 10.4 Gm. was given to a patient within seven days with no ill effects.

GUEST, Cincinnati.

GASTRIC SECRETION IN FEVER AND INFECTIOUS DISEASES. HSIAO-CH'IEN CHANG, J. Clin. Investigation **12**:155 (Jan.) 1933.

Gastric secretion from the stomach during fasting was examined during the first twenty minutes after the administration of 0.5 mg. of histamine (ergamine acid phosphate). Data for 106 Chinese patients with fever due to more than twelve different conditions were compared with data for normal afebrile Chinese. There was an inverse relationship between the acidity of the gastric juice and the temperature, this inverse relationship being expressed by a negative coefficient of correlation (-0.500 ± 0.052). The total chloride and the volume of secretion showed a similar but less marked change. Factors other than temperature apparently played no important rôle. Ninety per cent of the patients reexamined during convalescence recovered normal gastric function soon after the disappearance of fever.

GUEST, Cincinnati.

LOCALIZED OSTEITIS FIBROSA. P. N. RAY, J. Indiana M. A. **2**:246 (Feb.) 1933.

The author briefly discusses the characteristic features of localized osteitis fibrosa. He reports the case of a patient with spontaneous fracture who was successfully treated by osteoclasis and immobilization.

GONCE, Madison, Wis.

ERYTHROBLASTIC ANEMIA: CASE REPORT. DAVID W. PARKER, New England J. Med. **208**:1147 (June 1) 1933.

This rare disease of the blood in childhood has been described by Cooley. In none of the reported cases have the patients lived beyond childhood.

A case is described in a boy, aged 6 years, who complained of weakness, dyspnea on exertion, headaches and nausea and vomiting after eating. He had never vomited blood. The patient was 12 pounds (5.4 Kg.) under normal weight. The skin had a peculiar lemon color. The sclerae were yellow, and the spleen was enlarged. The red blood cells numbered 2,496,000, with 42.5 per cent hemoglobin. The white blood cells numbered 9,400. There were many nucleated red cells, poikilocytosis and no reticulated red cells. The urine was negative for bile. The Wassermann reaction was negative. A blood transfusion was given, and the spleen was removed. The patient made a good recovery. The pathologic diagnosis was Gaucher's splenomegaly. About six months later the symptoms of weakness and of yellow skin appeared. There were 1,200,000 red blood cells, with 10 per cent hemoglobin (Dare), 6,800 nucleated red cells and 6 per cent reticulocytes. The icteric index was 60. The general condition was extremely grave. The patient had an irregular fever as high as 106 F.; the blood pressure was 70 systolic and 0 diastolic. The family refused to have a blood transfusion and autopsy performed. Another child in the family, aged 3 years, has the same disease.

GENGENBACH, Denver.

THE SOCIAL PROBLEM OF THE CHILD WITH HEART DISEASE AS SEEN IN THE CARDIAC CLINICS OF THE MASSACHUSETTS GENERAL HOSPITAL. EDITH MORTIMER TERRY, New England J. Med. **209**:141 (July 20) 1933.

To turn the usual "don'ts" into "do's" for patients with heart disease; to help balance the disability of the children by interpreting their condition to them and to the parents; by opening out for them new interests, and by giving them opportunity to serve as well as to be served, in addition to seeing that the treatment prescribed by the physicians is carried out, is the *raison d'être* of the clinics for heart disease of the Massachusetts General Hospital.

Each patient is followed individually, and his problem is explained to him and to his parents. There are a Mother's Club and an In-Bed-Club as care in the home is preferred when possible. The occupational therapeutist and the librarian make contacts with all patients in the hospital; school work is given to older children to keep them up in their studies, and a physician and a social worker follow them into their homes. When adjustment at home is impossible, the children are sent to a convalescent home or are placed in foster-homes.

Actual care in bed is rendered by the community health service or by visiting nurses. There is also an adolescent clinic, a difficult group to handle, where educational and vocational work is emphasized, with the advice of the Child Guidance Clinic.

GENGENBACH, Denver.

THE DIAGNOSIS AND TREATMENT OF SECONDARY ANEMIA. WILLIAM P. MURPHY, New England J. Med. **209**:331 (Aug. 17) 1933.

Therapeutically, transfusions of blood are advised for quickest effect after acute or chronic hemorrhage, and before serious operations if anemia is already present.

Ferric ammonium citrate in large doses and pills of ferrous carbonate in very large (double) dosage have been proved of value in treating the secondary anemias that will respond to therapy.

Liver or liver extract (the latter better administered intramuscularly), especially with large doses of iron taken orally, is effective.

Copper, usually found in adequate amount in properly balanced diet or as a contaminant of iron salts, is usually provided in the properly balanced diet.

Arsenic, except for its general tonic effect or as an accessory treatment in leukemia, is not required.

Hydrochloric acid may be desirable in treatment of idiopathic hypochromemia in cases in which the natural acid of the stomach has been diminished. A diet which includes generous amounts of fruits, leafy vegetables, red muscle meat, liver and eggs should be recommended for all persons with anemia.

GENGENBACH, Denver.

SPLENOMEGALY: A CLINICAL CONSIDERATION. LESLIE L. NUNN, Northwest Med. **32**:111 (March) 1933.

The author considers a number of recent contributions to the knowledge of the function of the spleen, the classification of splenomegalies and their differentiation, and the indications for splenectomy and its prognosis.

SCOTT, Philadelphia.

THICKENING OF THE TERMINAL ILEUM WITH MESENTERIC ADENITIS IN CHILDREN. E. W. ROCKEY, Northwest Med. **32**:145 (April) 1933.

Four cases are reported. In each there were pain on the right side of the abdomen and leukocytosis, but no vomiting. A preoperative diagnosis of acute appendicitis was made in each case but was confirmed neither by findings at operation nor by histologic examination. A febrile period of from days to weeks followed operation. At operation a thickening of the terminal ileum was found, as well as enlargement of the mesenteric glands in that region. Since operation the patients have remained in good health.

SCOTT, Philadelphia.

ACUTE OSTEOMYELITIS IN CHILDREN. CECIL P. G. WAKELEY, Brit. M. J. **2**:752 (Oct. 22) 1932.

The author's conclusions are as follows:

"1. Osteomyelitis in children is a disappearing disease.

"2. The disease is not so fulminating as formerly, and that is due to the fact that the general health of the children is better.

"3. Trauma plays little or no part in the causation of the condition.

"4. Early drainage is the essential treatment."

ROYSTER, University, Va.

A CASE OF MALIGNANT THYMOMA. MARGARET LESLIE and WILLIAM S. BELL, Brit. M. J. **2**:1006 (Dec. 3) 1932.

A case of malignant thymoma is reported, with the results of postmortem examination, both macroscopic and microscopic, and a brief discussion as to the differential diagnosis.

ROYSTER, University, Va.

THE VALUE OF SALICYLATES IN THE PREVENTION OF RHEUMATIC RELAPSES. C. BRUCE PERRY, Lancet **1**:861 (April 22) 1933.

This is a study of forty-one children who had suffered with rheumatic heart disease. Relapses of a rheumatic nature were observed in 12.1 per cent of the patients treated with salicylates, as compared with 17.9 per cent of the controls. The author concludes that his series of patients shows little or no evidence that the prolonged administration of salicylates is of value in preventing relapses in rheumatic children.

LANGMANN, New York.

DIVERTICULA OF THE PHARYNX AND OESOPHAGUS. R. W. RAVEN, Lancet **1**:1011 (May 13) 1933.

Congenital diverticula of the pharynx and the esophagus are briefly discussed, the major part of the article being devoted to acquired diverticula.

LANGMANN, New York.

LIPODYSTROPHY. T. PEARSE WILLIAMS, Proc. Roy. Soc. Med. **26**:515 (March) 1933.

The mother of the patient noticed that the child's face was becoming thin for a year and a half before she took her to the clinic. On examination it was noticed that there was wasting of fat in the face, thorax and abdomen, and to a lesser degree in the arms. The buttocks and the thighs were fairly well covered. The weight and height were below the average for the patient's age.

WILLIAMSON, New Orleans.

CONGENITAL TUMORS: CASE FOR DIAGNOSIS. W. N. GOLDSMITH, Proc. Roy. Soc. Med. **26**:747 (April) 1933.

A baby, 8 months old, was taken to the hospital because of a tumor on the right shoulder about 1 inch (2 cm.) in diameter, of a fawn or mauve color. On the summit were two red, ulcerated areas which at first were fungating, bleeding growths. Around the main tumor were a few tiny outlying nodules deep in the cutis. On the left buttock were a large number of brown or mauve macules about the size of a split pea. The Wassermann reaction was negative. Biopsies were performed, and sections from the tumors were made. The histologic report and the author's various diagnoses are given.

WILLIAMSON, New Orleans.

NEW GROWTH ON FACE. R. A. RAMSAY, Proc. Roy. Soc. Med. **26**:1008 (June) 1933.

The patient, a girl of 4 months, was taken to the hospital on account of a swelling on the right side of the face over the parotid gland. It was painless, soft and ill defined, and the surface was bluish. The tumor was explored and found to be vascular.

WILLIAMSON, New Orleans.

LYMPHADENOSIS COMMENCING WITH CLINICAL PICTURE OF HYPOPLASTIC ANEMIA. F. PARKES WEBER and W. WEISSWANGE, Proc. Roy. Soc. Med. **26**:1012 (June) 1933.

A case of lymphadenosis was reported in a boy 11 years of age. A chart of weekly blood counts is given. The spleen and liver were at no time enlarged, although the lymphatic glands in the axillae, groins and neck were slightly enlarged. He suffered from epistaxis.

WILLIAMSON, New Orleans.

PERSISTENT PNEUMOTHORAX AFTER POST PNEUMONIC EMPYEMA. F. PARKES WEBER and W. WEISSWANGE, Proc. Roy. Soc. Med. **26**:1014 (June) 1933.

The patient, a boy, 1½ years of age, had measles at 6 months, followed by bronchopneumonia. He remained well from that time until he was admitted to the hospital suffering from bronchopneumonia which was followed by an empyema. The pus obtained by the exploring syringe contained pneumococci and staphylococci. Fifteen days later roentgen examination showed that the empyema had given place to a pneumothorax which persisted for some time.

WILLIAMSON, New Orleans.

HYPOGLYCAEMIA: CRITICAL REVIEW. G. M. WANCHOPE, Quart. J. Med. **2**:117 (Jan.) 1933.

In this comprehensive review of the subject of hypoglycemia the author fully discusses the many aspects of the subject. Experimental hypoglycemia, as well as the clinical conditions associated with the condition, is particularly well covered. An excellent bibliography is appended.

BRADFORD, Rochester, N. Y.

STUDIES ON THE RESPIRATORY EXCHANGE AND THE BASAL METABOLISM IN DIABETES. F. RATHERY, ANDRÉE PLANTEFOL and LUOIEN PLANTEFOL, Ann. de physiol. **9**:139, 1933.

The basal metabolism of patients with diabetes averaged 5 per cent above normal. It was much higher in the malnourished patients than in one of normal weight. Treatment with insulin reduced the metabolism to normal. This reduction was due not to an actual lowering of metabolism but to an increase in weight and consequently to an increase in body surface. The respiratory quotient in persons with diabetes averaged 1.76. The action of insulin on the respiratory quotient was variable, elevating it in some cases and having no effect in others. The ingestion of 50 Gm. of dextrose elevated the respiratory quotient slightly in some, lowered it in others, or had no effect at all in still others. The basal metabolism was not appreciably modified by the ingestion of dextrose in the majority of cases.

One of the most striking facts was the lowering of metabolism which followed the ingestion of dextrose in some cases. The authors believe that it indicates a particular form of diabetes.

The authors conclude that from their studies of the respiratory quotient, basal metabolism and reaction to the ingestion of dextrose in patients with diabetes treated with insulin, there are marked individual differences in the efficacy of insulin. In some cases there is a clearcut, positive action of insulin in its ability to reduce the basal metabolism and increase the respiratory quotient. In contrast, there are cases in which insulin has no effect or in which it manifests opposite reactions, i. e., lowers the respiratory quotient and increases the basal metabolism. It would seem that certain persons with diabetes possess a true "insulin resistance." The authors also believe that their studies indicate that prolonged treatment with insulin can bring about a permanent improvement in carbohydrated metabolism, at least in some cases.

BUDSON, Detroit.

LATENT HELMINTHIASIS IN CHILDREN. D. ANZIL, Riv. di clin. pediat. **31**:273 (March) 1933.

The author examined the feces of 100 children who were in the pediatric clinic in Florence for various diseases. Fifty-four per cent showed ova. The percentage varied from 23 in babies to 69 in older children. Practically none of the children had symptoms of helminthiasis. Trichocephalus was found in 35 per cent of the cases, Ascaris in 26 per cent and Oxyuris in 4 per cent.

HIGGINS, Boston.

MEDIASTINAL PLEURISY SECONDARY TO HODGKIN'S DISEASE. J. MARIA MACERA and BERNARDO R. MESSINA, Arch. argent. de pediat. **3**:707 (Nov.) 1932.

This condition occurred in a boy, aged 12 years. Persistent fever, bilateral shadows in the mediastinal region and mediastinal pleuritis, coupled with an intensely positive Mantoux reaction, strongly suggested tuberculosis. Biopsy of one of the enlarged axillary glands established the diagnosis of Hodgkin's disease.

SCHLUTZ, Chicago.

PERIFOCAL INFILTRATIONS. MAMERTO ACUNA and AUGUSTIN N. ACCINELLI, Arch. argent. de pediat. **4**:1 (Jan.) 1933.

In the opinion of the authors, the tuberculous nature of a pulmonary infiltrative process can be definitely established only if there are an adequate family history and an intensely positive Mantoux test and if the evolution of the process is progressive.

An insidious beginning, the absence of practically all abnormal clinical findings, fairly massive pulmonary shadows, continued well-being of the patient, slow progress of the condition and ultimate complete recovery point to a perifocal non-tuberculous infection. A report of several cases illustrates this point.

SCHLUTZ, Chicago.

ULCERATIVE COLITIS. Y. YNCLAN and E. DÍAZ ORERO, Arch. de med. inf. **1**:251 (Sept.) 1932.

In autopsy studies of a case of amebic dysentery, the authors found that perforation is favored by secondary infection. The infection with amebas takes place at the top of the follicle, and secondary invasion in the colon is thereby favored. Repeated search for the ameba is necessary, and an early positive diagnosis is of great value, as secondary infections may thereby be avoided. When a secondary infection develops, emetine does not impede the process.

SANFORD, Chicago.

THE TREATMENT OF ARTICULAR RHEUMATISM IN CHILDREN. J. A. BAUZA, Arch. urug. de med., cir. y especialid. **3**:117 (July) 1933.

The diet of children with articular rheumatism should consist of cereals and fruits. During the convalescent stage, proteins may be added slowly. Frequent rubs of alcohol heated to 50 or 60 C. are beneficial. Locally, a 10 per cent ointment of sulphonated bitumen, N. F., gives relief. For the active treatment, salicylates are given at the rate of 0.50 cg. a day. Adjuvants are nux vomica, and quinine. As complementary treatment, the author gives acriflavine hydrochloride intravenously, in doses of from 15 to 20 cc. in a 0.5 per cent solution.

SANFORD, Chicago.

PROMPT SPECIFIC RELIEF OF CERTAIN INTESTINAL PAINS. E. ESCOMEL, Crón. méd., Lima **49**:195 (July) 1932.

For nonhemorrhagic diarrhea with an acid reaction in infants, whether or not the evacuations are green or grumous, without changing the diet the author administers every two hours from 6 to 12 grains (0.3 to 0.7 Gm.) of chalk precipitated in mucilage.

Alkaline diarrhea, if not promptly relieved, presents features of gravity which may lead to athrepsia and death. The administration of mild mercurous chloride should not be delayed. For nourishment, a teaspoonful of lactose may be given in warm water every quarter of an hour, preceded, if there is vomiting, by five minutes application of a sinapism over the stomach. On the second and third days 2 or 3 Gm. of lactic acid should be given every two hours, and on the fourth day this may be supplanted by precipitated chalk.

When there is vomiting associated with acetone or diacetic acid in the urine, sodium citrate should be alternated with sodium bicarbonate. Rarely is it necessary to resort to epinephrine or insulin for more certain control. On the third day the administration of precipitated chalk may be begun if vomiting has ceased.

VINTON, Brooklyn.

SPECIFIC TREATMENT OF VENEREAL PAPILLOMA WITH TUIA OCCIDENTALIS. A. FRANCA, Rev. brasil. de pediat. **1**:33 (April) 1933.

Tincture of Tuia was applied locally to a venereal papilloma in a boy of 16 years. The treatment was successful. The author believes that this is a considerable improvement over the accepted methods of cautery or curettement. As he expresses it, it is "a homeopathic remedy, applied allopathically."

SANFORD, Chicago.

ABSCESS OF THE LUNG AND PULMONARY GANGRENE IN CHILDHOOD. HANS-ULRICH KÖTTGEN, Arch. f. Kinderh. **99**:131 (May 30) 1933.

Four cases of abscess of the lung in children are reported, with a clinical discussion and a brief review of the literature on this subject. The etiologic factors in abscess of the lung may be divided into three groups: first, aspiration of a foreign body, vomitus or of matter during tonsillectomy; second, pneumonia and

bronchiectasis, and, third, metastatic infections of the blood stream. The causative bacteria include pneumococci, streptococci, diphtheria bacilli, anaerobic bacteria and Vincent's organisms. The diagnosis and treatment vary greatly and depend on the findings and course in each case. In two of the author's patients rapid improvement followed the use of diathermy of short wavelength directed to the gangrenous region. It is probable that this condition is more frequent in children than has been recognized.

LEMASTER, Evanston, Ill.

CLINICAL SIGNIFICANCE OF AMIDOPYRINE-FAST FEVERS IN DISEASES OF INFANTS AND SMALL CHILDREN; GRIP AND PNEUMONIA. G. PETRANYI, Arch. f. Kinderh. **99**:145 (May 30) 1933.

A marked reduction in fever was regularly observed in several hundred infants and small children who were treated with large doses of amidopyrine during the course of grippal infections of the upper respiratory tract and pneumonia. Patients in whom amidopyrine failed to lower the body temperature showed a grave toxic condition with a poor prognosis. The onset of complications could be predicted very early by recrudescence of fever in spite of the continuous administration of amidopyrine.

LEMASTER, Evanston, Ill.

GONORRHEA IN CHILDHOOD: II. CLINIC OF THE GENITAL AND PARAGENITAL PROCESSES. LÓSZLÓ VON DOBSZAY, Arch. f. Kinderh. **99**:171 (May 30) 1933.

In a series of cases of vulvovaginitis, urethritis was found in one third of the patients and proctitis in almost one fifth. Involvement of the uterus, the tubes or Bartholin's glands was rarely seen in girls before puberty. The author believes that the paragenital localization of gonorrhea in children is much more frequent than has been recognized and that when it does occur the course of treatment necessary for cure is much longer than in uncomplicated vulvovaginitis.

LEMASTER, Evanston, Ill.

PATHOGENESIS OF ACETONEMIC VOMITING. M. WEICHSEL, Monatschr. f. Kinderh. **58**:9 (May) 1933.

The author reports simple clinical experiments which seem unusually interesting. It has generally been considered that cyclic vomiting in children results from some type of ketosis. Weichsel reports observations on four children suffering with typical attacks. In the interim he kept them for forty hours on a diet low in carbohydrate and high in fat. Although ketones appeared in the urine, no child vomited. He reports these experiments as arguments against the commonly held theory.

GERSTLEY, Chicago.

PROGNOSIS OF INTESTINAL INFANTILISM. W. COURTIN, Monatschr. f. Kinderh. **58**:39 (May) 1933.

The author reports follow up studies on thirty-four patients with celiac disease. He discusses the symptomatology, system by system—as manifested in the skeleton, musculature, the intestinal functions, growth, mentality and so forth. Of the thirty-four patients, ten died. The remainder made good recoveries and eventually showed no variations from the normal.

GERSTLEY, Chicago.

THYROID ENLARGEMENT IN THE SCHOOL CHILDREN OF SILESIA. S. SAMELSON, Monatschr. f. Kinderh. **58**:48 (May) 1933.

In Silesia there seem to be three goiter zones. In the mountains, goiter is frequent. In the lower foothills goiter is still common but seems to undergo a spontaneous improvement. In the lowlands, particularly in the city where there is better controlled prophylaxis, the percentage of incidence has dropped from 30 to 5.

GERSTLEY, Chicago.

CLINICAL DISCUSSION OF STILL'S DISEASE AND CHRONIC ARTHRITIS. HERBERT AEHLE, Montschr. f. Kinderh. **58**:57 (May) 1933.

Still's disease begins at the time of the second dentition with a periarticular change involving the small joints and never progressing to the formation of pus. Simultaneously there may be continuous fever or periodic attacks associated with enlargement of the spleen and general adenopathy. Adhesive pericarditis rather than valvular involvement is not uncommon. The blood shows anemia and leukopenia. A rash, either morbilliform or urticarial, may be one of the early symptoms. Roentgen examination shows atrophy of the surface of the bones and joints with no destruction or involvement of the cartilage.

Chronic rheumatism is much like Still's disease although fever, adenopathy and enlargement of the spleen are much less common. Involvement of the joints is insidious, often with no early symptoms. The large joints are involved equally with the smaller ones. In contrast to Still's disease, aspiration of the joints reveals bits of cartilage. The roentgenogram confirms the actual destruction of cartilage. Involvement of the heart is uncommon, as are changes in the blood.

Bessau divides chronic rheumatism into two groups on the basis of the findings on aspiration of the joints: (1) leukocytic and (2) lymphocytic.

The leukocytic form is found chiefly in Still's disease and suggests an insidious sepsis, while the lymphocytic form is found in chronic polyarthritis.

Aehle reports twelve cases which, on the basis of Bessau's plan, he divides into five cases of Still's disease, four cases of chronic arthritis and three unclassified cases.

The prognosis is better in Still's disease than in polyarthritis.

GERSTLEY, Chicago.

DIABETES IN CHILDHOOD. W. DÖHMANN, München. med. Wchnschr. **79**:2029 (Dec. 16) 1932.

Diabetic persons have a congenital impairment of function of the pancreatic cells which produce insulin. Twenty-five per cent of cases of diabetes show a familial occurrence of the disease in at least three generations. That the onset of diabetes in children is more frequent in two age groups was originally observed by Pirquet. Among Döhmann's patients, the onset in 48 per cent was between the ages of 3 and 6 years, in 13 per cent between 7 and 10 years and in 39 per cent between 11 and 14 years. Periods of rapid growth do not coincide with the time that diabetes becomes evident clinically. Döhmann believes that these periods are characterized by pronounced changes in the endocrine glands which may make latent diabetes manifest.

Diets relatively high in fat are used. The author warns against making the diet unpalatable by reducing the carbohydrate too much. It is better to give a few more units of insulin and a little more carbohydrate. The treatment for coma is the same as that in general use in the United States. During intercurrent infections the child's appetite is usually impaired. The author decreases the protein and fat and increases the carbohydrate in the diet. The dosage of insulin is temporarily increased.

The author advises against the use of special diabetic foods as well as of insulin substitutes which can be taken by mouth. Exercise is advisable since it increases carbohydrate metabolism and reduces the amount of insulin required. It is important to avoid making the child "sick-conscious." Hypoglycemic reactions in children are frequently manifested by psychic changes, which are more or less characteristic in each person. When the blood sugar is moderately low there may be irritability, misbehavior or some breach of discipline; when the blood sugar is greatly reduced there may be confusion states or even hysterical manifestations.

Unfortunately many diabetic children die in Germany because there is not enough money to pay for the necessary food or insulin or for proper hospitalization.

The author points out the injustice in failing to provide funds for the care of diabetic children who would make useful adults while considerable money and energy are expended in the care of cretins, mongolism idiots and other persons with hopeless mental defects.

BRAHDY, Mount Vernon, N. Y.

GLYCOGEN DISEASE (HEPATOMEGALIA GLYCOGENETICA OF VON GIERKE). L. SCHALL, München. med. Wchnschr. **79**:2078 (Dec. 23) 1932.

Schall reports three cases of hepatomegalia glycogenetica in children aged 8 years, 4 years and 1 year, respectively. Similar cases were originally described by Wagner and his associates and by Snapper and van Creveld. The first impression when one sees a child with this disease may be that the condition is distrophia adiposa genitalis. The most important symptoms are: (1) enlargement of the liver, observed frequently in infancy (the enlargement is due to glycogen stasis); (2) hypoglycemia without clinical manifestations (repeated estimations of the glycogen in the blood varied between 19.5 and 50 mg. per hundred cubic centimeters), and (3) failure of the injection of epinephrine to mobilize glycogen. Less constant symptoms are obesity, ketonuria and weakness of the skeletal muscles. It seems that a functional disturbance of the liver glycogen is the primary cause of the disease.

BRAHDY, Mount Vernon, N. Y.

THROMBOPENIC PURPURA AFTER MEDICATION WITH IODINE. H. DENNIG, München. med. Wchnschr. **80**:562 (April 14) 1933.

Dennig observed the occurrence of thrombocytopenic purpura in two patients who had taken iodide salts and in another with alterations in iodine metabolism due to exophthalmic goiter. Idiosyncrasy to iodides is infrequent, but such patients should be warned not to take medicaments containing iodine.

BRAHDY, Mount Vernon, N. Y.

CLINICAL PICTURE AND THERAPY OF THROMBOCYTOPENIC PURPURA. H. BRÜHL, Ztschr. f. Kinderh. **54**:159, 1933.

Thirty-five cases of thrombocytopenia were studied by the author in the past eight years. Of these, ten were essential and twenty-five symptomatic. Three patients of the former and nineteen of the latter group died. The symptomatic cases were all associated with other diseases of the blood. Additional symptomatic cases occurred (two each) in tuberculosis and streptococcic sepsis.

The clinical observations were:

1. The Rumpel-Leede phenomenon was as frequently positive and negative as in other diseases.

2. The capillary bleeding time was increased in Werlhof's disease (essential thrombopenia), at times even when there were no clinical phenomena of bleeding.

3. The capillary resistance (Hecht bell test) was lowered. Normally, 150 mm. of mercury negative pressure is required to produce the phenomenon of blood diapedesis but only from 40 to 50 mm. of mercury was required to produce it in thrombocytopenia, which indicates a lessened resistance of the capillary wall.

4. In essential thrombopenia, capillary bleeding occurred internally as frequently as externally. Regional variations, however, existed in bleeding from the capillaries of the skin.

5. There was no direct parallelism between the fall in thrombocytes and the Rumpel-Leede phenomenon or between the thrombocyte count and the bleeding time.

6. There was a strong relationship between spontaneous bleeding and lowered retraction of the blood clot. Low retractions of the blood clot usually occurred at a critical level of 45,000 thrombocytes. They were, however, observed in three

cases of congenital atresia of the gallbladder with icterus, without a reduction in thrombocytes.

7. In the pathogenesis of essential thrombocytopenia, the platelets are of secondary importance. In 50 per cent of the cases studied there were no coordinate disturbances in the clotting, but changes in the permeability of the capillary walls. This is indicated by (1) the presence of petechiae, (2) decrease in the capillary resistance (bell test) and (3) the appearance of a red color in the skin after the injection of congo red (usually absent in normal persons).

8. Gelatin, calcium and nateina are therapeutically not efficacious. Good local hemostatics are of no avail in internal bleeding.

9. In four patients with severe thrombopenia and in one patient with hemoptosis, the injection of congo red intravenously produced hemostatic effects. Bleeding stopped in a few hours—at the latest, on the following day. The injections may be repeated after from two to six days.

10. Blood transfusion is only a temporary measure to replace lost blood, but it has no styptic action.

11. Irradiation of the spleen had no effect on the clinical picture or on the platelets. Irradiation of the long bones had no immediate effect, but the platelets rose after from six to ten days.

MORTALITY IN BRONCHOPNEUMONIA. N. J. SCHIERBECK, Acta pædiat. **14**:92 (Nov. 30) 1932.

In large cities equipped with pediatric hospitals it is generally assumed that young patients with pneumonia should be hospitalized as quickly as possible. Schierbeck, who practices among the poor in their own homes, asserts that when a child, or more particularly a young infant, is bundled up for the trip to the hospital he is often almost smothered in the attempt to shield him from the cold, and arrives only too frequently in a state of collapse; thereupon he is exposed to other children with infections of the respiratory tract harboring a variety of organisms, against which he is fortunate if he has any resistance. The statistics in hospitals for mortality are not altogether cheerful. Schierbeck tabulated the results in the cases of 383 patients with bronchopneumonia treated in one of the pediatric clinics of Copenhagen. The cases represented 14 per cent of the total admissions to the hospital, an index of the popularity of hospitalization for pneumonia. About half of the patients had been ill only one or two days at home, which shows that the local physicians were alert to refer the patients to the hospital at the earliest possible moment. Among the patients under 1 year of age, nearly two thirds were admitted within two days of the onset of symptoms. The total mortality was 25 per cent, but for the group of infants under 1 year of age, it was 37.5 per cent; among the patients admitted on the first day of illness, it was 54 per cent. This last figure may be interpreted as evidence of the severity of the infection in individual cases, but the harm that may be done to young patients by rushing them to the hospital is suggested by the fact that 61 per cent of the patients under 1 year of age who were admitted on the first day of illness died of pneumonia. Unfortunately, no statistics based on treatment of pneumonia at home are given, but the author places the burden of proof on those who advocate the admission of young patients to a hospital for severe respiratory infections.

MCINTOSH, New York.

INJURY TO THE HUMAN HEART RESULTING FROM EXPOSURE TO NATURAL OR ARTIFICIAL ULTRAVIOLET LIGHT. I. JUNDELL, G. SVEDENIUS and H. BJERLÖV, Acta pædiat. **14**:404 (April 28) 1933.

No injury of the heart could be detected by clinical or electrocardiographic examination in children subjected to intensive sunbaths, either with natural sunlight or with ultraviolet rays from the mercury vapor arc in quartz.

MCINTOSH, New York.

INJECTION OF IODIZED OIL INTO THE PERICARDIAL CAVITY IN A CASE OF PERICARDIAL EFFUSION. P. W. FRITSCH, Acta pædiat. **14**:412 (April 28) 1933.

Iodized poppy seed oil 40 per cent has previously been injected into the pericardium in cases of tuberculous pericarditis without untoward result and with possible benefit. The author's patient, a girl, 10½ years of age, suffered from rheumatic carditis, with pericardial and pleural effusions, pneumonia and cardiac decompensation; she seemed moribund. From the pericardial cavity 75 cc. of blood-stained fluid, containing leukocytes and pneumococci, was removed; 2 cc. of iodized oil was injected. A slow but satisfactory recovery ensued, so that she left the hospital free from symptoms although with a pronounced mitral lesion. Seven months later iodized oil was still visible in the pericardial cavity by roentgen examination.

McINTOSH, New York.

Nervous Diseases

ENCEPHALOGRAPHY IN CHILDREN: FURTHER OBSERVATIONS IN CHILDREN WITH FIXED LESIONS OF THE BRAIN. R. CANNON ELEY and EDWARD C. VOGT, Am. J. Roentgenol. **27**:686 (May) 1932.

Eley and Vogt consider adequate indications for encephalography to be: (1) inability to understand fully the existing conditions, (2) inability to offer definite information regarding prognosis, educational problems and, when necessary, proper disposition of the patient and (3) inability to demonstrate concrete and convincing evidence to the family. In expanding lesions of the brain with increased intracranial pressure, as evidenced by papilledema, the cracked-pot sound, and other usual signs, the introduction of air is obviously contraindicated. The technic is given in detail, and roentgenograms illustrating several conditions are shown. The conclusions are that encephalography is a valuable diagnostic procedure in the study of children with fixed lesions of the brain and that the information obtained warrants the risks involved. The judicious employment of this procedure should eventually lead to a better understanding and classification of such conditions as epilepsy, feeblemindedness and cerebral palsy occurring in children. From the encephalograms alone one is unable to determine the nature of the initial etiologic agent responsible for the ultimate gross pathologic changes.

STULIK, Chicago.

THE DISTURBANCES IN VISION AND IN VISUAL FIELDS AFTER VENTRICULOGRAPHY. CLEMENT B. MASSON, Bull. Neurol. Inst. New York **3**:190 (June) 1933.

Temporary blindness occurred in six of a hundred consecutive cases in which air was introduced into the ventricles after puncture of the occipital poles of the brain for roentgen examination. Three patients had normal fundi, and three had papilledema of from 2 to 4 diopters. In five patients vision was normal, or nearly so, and in one, it was reduced before ventriculography. One patient had a homonymous hemianopia, and one had contracted fields before the procedure. In three cases, there were indications of increased intracranial pressure.

In two patients, vision began to fail during the manipulations incident to the introduction of air; in the remaining four, it began to fail two, three, four and sixteen hours after the procedure. The amount of air introduced varied; some ventricles were partially and some were completely filled. A double Babinski reflex, which soon disappeared, developed in one patient. No other neurologic disturbances were noted.

In two cases, the reflex path for the contraction of the pupils to light was active during the period that vision was lost, and in one case the pupils were at

first widely dilated and did not contract even to light, while some vision remained. Notes were not complete on the other three cases.

Visual acuity was depressed to hand movements in two cases and was completely lost in the other four. In all of the patients the period of blindness lasted from twenty-one to seventy-two hours, four of the patients being operated on during the period. All of the patients eventually regained the visual acuity which they had possessed before ventriculography. It required from seven to thirty days for vision to return to normal (no definite figures are given) after the period of reduced vision.

The author feels that while the loss of vision in these cases was in some way connected with the puncture of the brain, he does not believe that the nature and situation of the cranial lesion, the introduction of air or the trauma to the occipital lobe by the actual puncture could be considered as the sole determining factors in any case.

W. F. DUGGAN. [ARCH. OPHTH.]

RESPIRATORY FAILURE AND THE DRINKER RESPIRATOR IN POLIOMYELITIS. E. SMITH, J. A. M. A. **100**:1666 (May 27) 1933.

Paralysis of the respiratory muscles may appear in twenty-four hours in any case of poliomyelitis with or without a rise in temperature. There is no need of waiting for a fully established picture of failure of the respiratory muscles to appear. When there is diminished vital capacity the patient should be placed in the respirator. The condition can be easily determined by the counting test. Ten centimeters of negative water pressure in the respirator is sufficient for children under 10 years of age. The respiratory rate of the machine should correspond to the normal respiratory rate of the patient. Immediate almost miraculous improvement follows the use of the respirator, but in spite of apparent improvement the prognosis should be withheld for five days. The ability to cough, not the ability to breathe freely without effort, is the indication for removal from the machine, for otherwise atelectasis and bronchopneumonia may develop.

BONAR, Salt Lake City.

BILATERAL ABDUCTOR PARALYSIS IN A TWO DAYS OLD INFANT. S. J. PEARLMAN, J. A. M. A. **101**:1150 (Oct. 7) 1933.

An infant, aged 2 days, with bilateral abductor paralysis of the vocal cords was treated by tracheotomy. Recovery followed.

BONAR, Salt Lake City.

OVERSUGGESTIBILITY IN JUVENILE DELINQUENCY. ALBERT S. BECKHAM, J. Abnorm. & Social Psychol. **28**:172 (June-Sept.) 1933.

Beckham believes that in juvenile delinquency oversuggestibility provides a promising field for study. It is frequently observed that strong suggestion exerts a marked influence on the behavior of youth. Observations in the juvenile court reveal that many aggressive delinquents are guided by the advice of others, particularly in stealing and in sexual misconduct. Suggestions emanating from gangsters and criminals, especially those of the robber type, play a peculiarly important rôle in the life of children. The oversuggestible boy or girl who comes in conflict with the law is usually considered unstable. Beckham believes that the prevention of delinquency lies in the responsiveness of the delinquent child to elders who are capable of reliving the life of youth or are willing to see from the child's point of view, not flaunting it in his face. Beckham also recommends supervised control of leisure and education in healthy mental attitudes, attention being paid to the control of emotions and the conditioning of habits.

ABRAMSON, New York.

INFLUENZAL MENINGITIS. THE RELATION OF AGE INCIDENCE TO THE BACTERICIDAL POWER OF BLOOD AGAINST THE CAUSAL ORGANISM. LEROY D. FOTHERGILL and JOYCE WRIGHT, J. Immunol. **24**:273 (April) 1933.

The authors present an explanation for the age incidence of influenzal meningitis. It is shown that about 80 per cent of the cases of this disease occur in children between 2 months and 2½ years of age. By means of a special technic the bactericidal power of blood from persons of various ages for a "smooth" meningitic strain of the influenza bacillus was studied. Blood of the umbilical cord and blood of infants during the first six weeks of life possessed considerable bactericidal power. This represents a passively acquired immunity from the mother, the antibody having passed the placental barrier. With rare exceptions, the blood of children between the ages of 2 months and 3 years has practically no bactericidal power. It is during this age period that the disease is very common. After the age of 3 the bactericidal power gradually rises and appears to be permanent in adult life. This probably represents an acquired active immunity. The bactericidal activity is due to a humoral antibody. Because of it, the bacteremic stage of the disease (which precedes meningitis) is prevented in those persons possessing the antibody.

AUTHORS' ABSTRACT, Boston.

EVERYDAY PSYCHOLOGY OF THE NORMAL CHILD. EDWARD A. STRECKER, Ment. Hyg. **17**:65 (Jan.) 1933.

The child must draw on the environment for the satisfaction of its psychologic needs; a deprivation or inadequacy of this psychic foodstuff will injure the child's personality. To develop a wholesome personality certain needs must be met—stimuli drawn for the most part from the postnatal environment. First of these is the need for physical motion; a child prevented from exploring the environment by movement will suffer a deficiency in the stream of incoming stimuli—and consequently will be mentally or emotionally retarded. A quiet boy or girl is a good, but not a sound, child. Second to motion is the group of influences embracing imitation, identification, idealization and suggestibility. The acquisition of ability to talk is, in normal children, largely a process of imitation. Since children are unable to make fine ethical distinctions, they add to their personality structures many layers of both good and bad qualities by this process. Probably the emotional force behind imitation is largely one of identification with the idealized parent or guardian. This tendency presents one of the most delicate problems in child guidance: the maintenance of the parent ideal. If the ideal crashes too soon, the child loses confidence and stability in his world; if it persists too long, the child becomes tragically dependent on the parent, teacher, or parent-surrogate. Less direct than imitation is the inclination toward certain behavior patterns produced by suggestibility.

The conditioning of reflexes deserves some consideration in child guidance. Much nervousness, indigestion, insomnia and enuresis represents bad conditioning. For example, bedtime may be associated with hilarity or excitement instead of peace and calm. Unsuccessful punishment is often the result of improper conditioning. Cruel, retaliative, delayed or promised-but-unfulfilled punishment is futile because it fails to associate, in time or proportion, the offense and the result. Distortions in the normal will-to-power are also responsible for many childhood behavior problems. For example, the transition from pampered convalescence to normal health may be difficult because of the swing to one extreme—deflation—or the other—overemphasis. In the first instance the child, brought harshly to realize that his days of power are over, is frightened and made permanently cynical or hard; in the latter instance the child is spoiled and made unreliant and dependent.

Curiosity is a normal and desirable childhood trait. It should be met by simple and truthful answers. Questions about sexual functions should be answered with the same casualness as meets all other questions. Another juvenile trait needing attention is the tendency toward savagery. This is a condensed replica of the

human savage state through which we have passed on the road to civilization. It is by proper exploitation of this quality that we may develop love of nature, courage, physical strength, fair competition and self-reliance. Since every adolescent sooner or later must enter into a competitive world, the desire to win, and to win fairly, should be inculcated early in life. Finally, that budding of the faculty of imagination—romancing—should be mixed with truthfulness yet received with respect.

These potentials must be fitted together skilfully to produce the wholesome personality. They form the stream of environment. And the environment of the child is in the hands of the adult.

DAVIDSON, Newark, N. J. [ARCH. NEUROL. & PSYCHIAT.]

WHY A CHILD REFUSES TO EAT. DOUGLAS P. ARNOLD, New York State J. Med. **33**:20 (Jan. 1) 1933.

Anorexia is a psychologic problem, and in order to prevent it all conflict over food must be avoided from the day of birth. Competitions for gaining weight should be avoided. The fat baby is not always the healthiest baby. When this paper was red, Arnold presented interesting motion pictures of infants and parents, to illustrate his points.

AIKMAN, Rochester, N. Y.

TUBEROUS SCLEROSIS AND ALLIED CONDITIONS. MACDONALD CRITCHLEY and C. J. C. CARL, Brain **55**:311 (Sept.) 1932.

Bourneville, in 1880, was perhaps the first to recognize tuberous sclerosis as a pathologic entity. Marks of psychopathy were found in the family history in thirteen cases. Symptomatically, in true epiloia the first abnormality is usually delay in development, the mental defect being obvious as a rule by the third year. Within the first decade cutaneous lesions appear. After puberty the general course is rapidly downward. The clinical course in the incomplete variant forms, formes frustes, may differ considerably. Most of the patients are undersized for their age, and stigmas of degeneracy are usually observed in those of low grade. The chief neurologic findings have been flat tumors or "phakomas" of the retinas, hypotonus in younger persons, which is replaced by rigidity in older patients, motor restlessness and occasional local paralysis. Critchley and Carl found the instance of cerebellar signs in only one case. Psychologically there is a combination of intellectual defect proper with a primitive form of psychosis (always catatonic schizophrenia). In the high grade patients, the psychosis manifests itself at or after the fifth year; in the low grade, deterioration begins earlier. The most important dermatologic lesion of the skin is the facial adenoma sebaceum.

Pathologically, whitish, slightly prominent areas are found, usually only in the cerebral hemispheres. The microscope shows marked anarchy in the stratification of the nerve cells, with regressive changes in the neurons themselves, and overgrowth of glia cells and foreign large cells.

Four clinical variants are proposed: (1) adenoma sebaceum alone; (2) adenoma sebaceum with epilepsy, but with no mental change; (3) adenoma sebaceum with symptoms of cereberal tumor, and (4) visceral tumor alone (including retinal tumors). Tuberous sclerosis may be regarded as (1) a hyperplastic disorder of the neuroglia originating during embryonic life or (2) a widespread metaplasia affecting mainly the ectodermal tissues. It is thought that the similarities between tuberous sclerosis and Recklinghausen's disease have perhaps been overemphasized.

MICHAELS, Boston. [ARCH. NEUROL. & PSYCHIAT.]

CHOREA: A SHORT STUDY OF 200 CASES. H. L. WALLACE, Edinburgh M. J. **40**:417 (Sept.) 1933.

Certain interesting features appear in the study of hospital records at the Royal Infirmary, going back ten years. The sex incidence of chorea is 2.7 to 1 for females, the average age for the girls entering the hospital being somewhat

higher than that for the boys. Fourteen and five-tenths per cent of the girls were above 16 years of age, and only 6.6 per cent of the boys. This deals only with the age on admission and not with the age on contracting the disease. Rheumatism in the family history was present in 18.7 per cent of the cases, previous rheumatism in the patient was reported in 45.6 per cent, and previous attacks of chorea in 18.6 per cent. Chorea followed scarlet fever in six instances; it appeared after diphtheria in four cases. Nervous shock seemed to have been an exciting cause in 26 per cent, but in about half of these cases rheumatism was superimposed.

On the belief that nervous instability is often associated with left-handedness, a study was made to see whether left-handed children are more prone to contract chorea. In fifty-three cases, the movements, excepting the facial jerkings, were present on one side of the body only. The heart was involved in 41.5 per cent of all the cases. The mortality rate was 2.7 per cent. Either violent chorea or cardiac involvement caused the six deaths.

NEFF, Kansas City, Mo.

TYPES OF MENTAL DEFICIENCY AND THEIR SOCIAL SIGNIFICANCE. E. O. LEWIS, J. Ment. Sc. **79**:298, 1933.

Mental deficiency is nothing but a variation from the normal in the range of mental equipment, and since the range of normal variation is not known, one should not assume that a mental defect is necessarily an evidence of abnormality. Mental deficiency that is abnormal belongs to a definitely organic pathologic group, which presents structural disease and abnormalities of the central nervous system. These cases should be called pathologic types. The person with mental deficiency who simply varies from his fellow man in intellectual equipment should be called a subcultural type. Lewis points out that the deficiency is only an extreme example of normal variation of mental endowment. There is no definite cleavage, but a close biologic kinship, between this group and the mass of normal persons. This is altogether different from the case of the so-called pathologic defective.

Such a classification as Lewis offers gives an opportunity to understand the social problems involved. The general conclusions about the subject at present are that most pathologic cases belong in the lower grades of deficiency, idiots or imbeciles, whereas most of the subcultural cases belong in the class of feeble-minded or what would be called in American terminology, "morons." The great majority of defectives belong to the subcultural group. The pathologic cases are evenly distributed among all the sections of the community. The subcultural type is concentrated to a large extent in that part of the community which is usually assisted by social agencies and which presents all types of social maladjustment like pauperism and slumdom. (This generalization by Lewis is probably not generally accepted by American students.)

Heredity is a more important factor in the production of subcultural types than in the production of pathologic types. When one finds several defective persons in one family they are usually of the subcultural types. Lewis points out that under modern conditions there is a tendency for the subcultural groups to be precipitated from the general life of the community. Modern conditions effect the exclusion of men and women with poor mental equipment. (This impression equally does not apply to American practice; with high development of industry there is an extra opportunity for the mentally defective person to do simple routine, monotonous, repetitive tasks.) Lewis believes that the subcultural types constitute greater social problems than the pathologic types, because in cases of the pathologic type the only procedure available is institutional treatment, whereas subcultural types may be adjusted in the community. He believes also that the same principles should be applied for the purification of the community as in the case of tuberculosis; by this he probably means eugenic control.

KASANIN, Howard, R. I. [ARCH. NEUROL. & PSYCHIAT.]

THE THYROID GLAND IN MENTAL DEFICIENCY: A HISTOLOGICAL STUDY. J. L. NEWMAN, J. Ment. Sc. **79**:464, 1933.

Newman reports a histologic study of the thyroid glands of ninety mentally deficient children between the ages of 1 and 19, who died at the Fountain Mental Hospital in England. In clinical analysis of the cases he uses Tredgold's classification of primary and secondary mental deficiency. By primary mental defect he means the conditions caused by some anomaly or defect of the germ plasm, while secondary mental deficiency is due to traumatic, toxic and infectious agents. Sixty-five cases were in the primary group. The author gives a thorough analysis of the cases from the point of view of the histologic picture, clinical analysis, age at death, state of nutrition and death. He emphasizes the extraordinary variations in the histologic picture in the so-called normal thyroids, and finds the same variation in the thyroids of mentally deficient children. No consistent findings were established correlating mental deficiency with a specific histologic abnormality of the thyroid gland. He conservatively remarks that there is evidence of qualitative and quantitative lack of parenchyma, suggesting a diminution of the function of the thyroid gland. The thyroid glands of children usually show a hyperplasia which is not seen in adults. The state of nutrition has no connection with the histologic appearance of the thyroid gland. There was no correlation between the thyroid and the thymus glands. The review of the subject occupies forty pages and is done with a great deal of care and thoroughness.

KASANIN, Howard, R. I. [ARCH. NEUROL. & PSYCHIAT.]

ETIOLOGY OF MONGOLIAN IDIOCY. A. SANTILLANA, Arch. de méd. d. enf. **36**:615 (Oct.) 1933.

Rejecting the numerous theories of causation advanced since Langdon Down in 1886 established mongolism as a definite clinical entity, the author, in a study of eight cases, reaches the conclusion that this condition may be described as an anomaly directly concerned with an exhausted reproductive system. He argues that various factors may operate to effect this condition such as age, consanguinity, multiple pregnancy, alcoholism, syphilis and defects of the germinal cells.

AMESSE, Denver.

MONGOLISM IN A FEMALE TWIN WITH A NORMAL BROTHER. G. MOURIQUAND and J. SCHOEN, Arch. de méd. d. enf. **36**:620 (Oct.) 1933.

Numerous observations of mongolian idiocy in twins have been reported; twenty-one cases are recorded in which, in different sexes, one infant was affected and the other was normal, while in twenty-four instances reported, twins of the same sex have shown one presenting the well known syndrome of this degenerative anomaly. The authors discuss the case of a female infant, 9 months of age, born one month prematurely of vigorous, middle-aged parents, who was brought to the clinic with a history of imperfect growth and development. Examination showed this baby to be a mongolian idiot, although its twin brother was quite normal.

AMESSE, Denver.

COMA AND HEMIPLEGIA DUE TO LOCALIZED SEROUS MENINGITIS. MARCEL FEVRE and JACQUES MAGDELAINE, Bull. Soc. de pédiat. de Paris **30**:484 (Oct. 18) 1932.

A girl, 4 years old, suddenly became comatose and showed signs of hemiplegia of the right side. Lumbar puncture gave negative results except that it demonstrated no change in the pressure of the spinal fluid after compression of the jugular vessels, indicating a block high up. A simple operation was done in which the left temporal bone was trephined and the dura punctured by means of a needle. A large quantity of clear cerebrospinal fluid was drained. It spurted from the

needle, showing markedly increased pressure, but showed nothing abnormal on laboratory test. The child regained consciousness two hours after the operation and made a rapid recovery. The left ear drum was incised and some serous discharge was obtained. On admission there was a history of a painful ear some time previously, but examination of the ears gave negative results.

BENJAMIN, Montreal, Canada.

COMPLETE SYNDROME OF THE LAST FOUR CRANIAL NERVES (COLLET) WITH PARALYSIS OF THE SYMPATHETIC OR SYNDROME OF THE PAROTIDEAN POSTERIOR SPACE (VILLARET). G. GALAND, J. de neurol. et de psychiat. **32**:723 (Oct.) 1932.

Galand reports the case of a boy in whom, following an injury to the skull which did not cause unconsciousness, there developed a cervical tumor on the right side and a protrusion of the right tonsil, but no associated tonsillitis. After three days there was a discharge of pus into the throat; on the following day still more pus was discharged, with a fall in temperature. Two days later, there was hematemesis, which recurred in eighteen hours. On the next day there was a pupillary inequality, with myosis on the right side, and deviation of the tongue to the right; the uvula was drawn to the left. A few hours later, the pain and cranial nerve involvements were more marked and were associated with the oculocardiac reflexes, and eventually with complete paralysis of the right vocal cord. This cranial nerve syndrome was first described by Collet after an injury in war. During the first few days hematemesis was the apparently important symptom, but this resulted from blood swallowed from the wound in the posterior pharyngeal wall, the hemorrhage coming from some vessels torn by the fracture of the skull.

WAGGONER, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

EFFECT OF ULTRAVIOLET RAY THERAPY ON NEUROMUSCULAR EXCITABILITY IN CHILDHOOD. M. PEHU, G. MORIN and A. RICHARD, J. de radiol. et d'électrol. **17**:227 (April) 1933.

The experiments of the authors led them to conclude that ultraviolet actinotherapy as at present administered has an effect on the neuromuscular excitability of children. Most frequently this is shown in diminished chronaxia. But it is not exceptional to meet increased chronaxia, and some muscles seem to escape any important alteration. Modification of the chronaxia varies at different stages of treatment and in accordance with numerous functional conditions not fully ascertained. These shifting varieties of excitability are probably connected with the equally variable and complex effects of the rays emitted by the mercury vapor lamp on the physicochemical properties of the blood plasma and on the vegetative nervous system. The practical conclusion is that, if possible, the chronaxia should be determined in children before ultraviolet irradiation is administered and at intervals during treatment in order that the results may be interpreted correctly.

VINTON, Brooklyn.

MEDICOPSYCHOLOGIC EXAMINATION OF MINOR DELINQUENTS IN THE DEPARTMENT OF THE SEINE. G. HEUYER, Rev. méd.-sociale de l'enf. **1**:101 (March-April) 1933.

The laws having to do with delinquent minors in the Department of the Seine are based on those embodying the American juvenile courts. Children under 13 years of age are not penally responsible; those from 13 to 18 are judged in ordinary courts, but may be placed on parole. A medical examination is not required by law, but since 1927 and 1928 it has been customary to give all juvenile offenders a complete medical and psychologic examination, including a study of the hereditary and social background. Five categories are recognized: (1) the normal child, who has been led into wrongdoing through his associations, (2) the

child with epilepsy or encephalitis, (3) the feebleminded child, (4) the unstable child who is a first offender and (5) the perverse, repeatedly delinquent child. Heuyer points out that it should not be necessary to wait until a crime has been committed before recognizing many of these conditions. The more frequent use of neuropsychiatric consultations in schools and dispensaries and a more adequate supervision of the abnormal child would do much toward improving conditions.

LESLIE, Chicago.

BEHAVIOR OF UREA, URIC ACID AND CHOLESTEROL OF THE BLOOD IN THE COURSE OF MENINGO-ENCEPHALOPATHIES. N. LOLLI, Riv. di pat. nerv. **41**:96 (Jan.-Feb.) 1933.

Lolli reports on the behavior of urea, uric acid and cholesterol in the circulating blood in twenty-three cases of involvement of the central nervous system (hemorrhage in the brain, tumor of the brain, influenza, meningo-encephalitis, purulent meningitis, influenza meningitis, cerebral embolism and other conditions). The urea, uric acid and cholesterol in the blood and the urea and uric acid in the urine are often increased. The modifications in the rate of urea have proved to be independent of involvement of the kidney or of a febrile reaction. There was an oscillation in the quantity of these components proportionate to the clinical oscillation of the disease; with recovery from the cerebral process there was a definite lowering of the figures.

Lolli thinks that there must be cerebral centers which regulate most of the chemical components of the blood. Therefore, he has studied experimentally the influence of lesions of the cortex and of the fourth ventricle in relation to variations of these components; he concludes that particularly punctures of the fourth ventricle produce definite variations in urea and cholesterol. At times these variations are even independent of the puncture itself and appear as a result of decompression following removal of fluid from the fourth ventricle. Experimental lesions of the cortex have caused slight but not constant variations. Probably the lesions act indirectly on the various regulating centers of the rhombencephalon.

FERRARO, New York. [ARCH. NEUROL. & PSYCHIAT.]

A CASE OF PNEUMOCOCCIC MENINGITIS. OSCAR JULIO MONTANARO, Rev. méd. latino-am. **18**:1186 (July) 1933.

The author believes that in cases of purulent meningitis one should use a mixture of equal parts of antimeningococcic serum and antipneumococcic serum, while awaiting the report of the laboratory examination of the spinal fluid. A case of meningitis in a child, aged 5 years, is reported, in which he used both types of serum intraspinally and intramuscularly, after a clinical diagnosis of purulent meningitis was made. On the following day pneumococci were reported to be abundant in the spinal fluid removed at the first puncture. Thereafter, the patient received only antipneumococcic serum.

DWYER, Kansas City, Mo.

SIGNIFICANCE OF DIRECT VENTRICULOGRAPHY FOR LOCALIZATION OF BRAIN TUMORS WITH SPECIAL REFERENCE TO TUMORS OF THE POSTERIOR FOSSA. F. HILPERT, Arch. f. Psychiat. **98**:388 (Dec.) 1932.

In an introduction Hilpert discusses the difficulties that are presented in clinical attempts at diagnosis of the localization of tumors of the brain in general, but especially of those of the posterior fossa. The effects of the general increase in pressure and remote effects of the tumor make it difficult to find any special set of symptoms that are pathognomonic for tumors of the posterior fossa. The most reliable symptoms are: (1) decrease of vestibular irritability; (2) compulsive postures of the head; (3) partial congestion syndromes which manifest themselves in positive Nonne-Apelt, Pandy and Weichbrodt reactions, normal cell count, and a mastic reaction of syphilitic type; (4) tachycardia in the presence of signs of

increased intracranial pressure. But even these symptoms are not altogether reliable, and Hilpert is of the opinion that the most important single diagnostic criterion is offered by direct ventriculography. This is to be preferred to encephalography because the results are better and there is less danger in tumors of this type.

Twenty-six cases are reported in which direct ventriculography was undertaken; in most of them the results were highly satisfactory. The author describes the technic that he uses; he is of the opinion that the amount of air injected does not have any essential influence on the results, but that the most favorable pictures were obtained when the amount of air injected was four-fifths that of the fluid withdrawn.

MALAMUD, Iowa City. [ARCH. NEUROL. & PSYCHIAT.]

PERMEABILITY OF THE MENINGES. YOSHIRO YAMAOKA, Monatschr. f. Kinderh. **58**:391, 1933.

The writer gave dogs 8 weeks old intracardial injections of various pigments, trying to trace them through the nervous system. The results were confusing, owing presumably to the fact that different body tissues had different effects on the pigments.

GERSTLEY, Chicago.

ROENTGENOLOGIC DIAGNOSIS OF TUMORS OF THE THIRD VENTRICLE. K. ALBRECHT, Monatschr. f. Psychiat. u. Neurol. **79**:136 (June) 1931.

Albrecht reports a number of cases in which a diagnosis of tumor of the third ventricle was made by means of ventriculograms. Lateral exposures of the skull were studied. Under normal circumstances the third ventricle does not hold sufficient air to be well defined in lateral views. In cases of hydrocephalus due to atrophy of the brain it becomes symmetrically enlarged, appearing similar in shape to a segment of an orange with the convex side upward. Hydrocephalus produced by occlusion leads to enlargement which is greatest at the thinnest parts of the ventricular walls, that is, anteriorly where the wall is formed by the lamina terminalis and posteriorly in the region of the recessus infundibuli. If a tumor is present in the third ventricle, the shape of the ventricle may be altered, and the outline of the tumor may be seen encroaching on the lumen. In order to obtain satisfactory plates it was necessary to remove more than 50 per cent of the ventricular fluid. With the patient's head placed laterally, fluid from the upper ventricle was removed and replaced with air until air could be aspirated from the opposite lateral ventricle. In this manner proper filling of the third ventricle was assured.

ROTHSCHILD, Foxborough, Mass. [ARCH. NEUROL. & PSYCHIAT.]

VASCULAR CHANGES OF THE CENTRAL NERVOUS SYSTEM IN RHEUMATIC CHOREA. K. VON SANTHA, Virchows Arch. f. path. Anat. **287**:405, 1932.

In a girl, 15 years of age, who was suffering from chorea, complete muscular paralysis of all the extremities developed. She died sixteen days after the onset of the disease. Autopsy revealed, besides acute endocarditis and pneumonia, remarkable changes in the brain. The significant features were thrombosis, obliteration and recanalization of the small vessels of the pia mater. There were hyperemia, capillary endarteritis and small necrotic areas in the cortex and subcortex.

SAPHIR, Chicago. [ARCH. PATH.]

A RARE CASE OF ISOLATED FACIAL PARESIS IN AN INFANT. M. KINCZLER, Orvosi hetil. **76**:979 (Oct. 29) 1932.

An infant 6½ months old showed a right-sided facial paralysis associated with cough and fever. A solitary tubercle is considered its cause and is assumed to lie probably at the level of the nucleus of the facial nerve or in a place near

its intracranial trunk. Roentgen examination revealed miliary tuberculosis of the lungs. The facial paralysis continued to be isolated; no other cerebral nerves were affected, and there was an absence of meningeal symptoms. Death occurred from pneumonia and cardiac failure.

At autopsy a caseous tubercle the size of a bean was found in the brain on the left side at the level of the large cerebral nuclei, at the caudal portion of the nucleus caudatus. A second tubercle was detected on the floor of the fourth cerebral ventricle. Internal hydrocephalus was present but no meningitis. The nuclei of the facial nerve had been destroyed by the tubercle.

N. BLATT. [ARCH. OPHTH.]

EPIDEMIC MENINGISM. MARIE MIKES, Časop. lék. česk. **71**:105 (Jan. 22) 1932.

A review of the literature is followed by reports of three cases. This severe but self-limited disease has signs and symptoms which include: severe headache, vomiting, vertigo, a rigid and painful neck, an indefinite Kernig sign, no salivation or fixation of pupils, a neutrophilic leukocytosis, a slightly positive Pandy test, normal chlorides, lymphocytes predominating in the spinal fluid, negative cultures in all cases and a negative Ravaut test. One patient had associated, active tuberculosis. Pelnar thinks that the etiologic agent may be similar to that of epidemic encephalitis.

STULIK, Chicago.

THE TREATMENT OF CHOREA. D. M. ZALKAN and F. M. LICITZA, Vrach. delo, 1933, no. 2, p. 75.

Zalkan and Licitza discuss the present knowledge of the treatment of chorea and present some of their own observations and views. In their experience the most spectacular results in aborting the course of even severe chorea were observed in the process of a superimposed or parallel infection. In five patients observed by them, in four of whom grip developed and in one, furunculosis, the choreiform movements subsided entirely in from one to four days, the symptoms disappearing sooner in the cases in which the febrile reaction was highest. The next best results were obtained by the use of typhoid vaccine which seemed to be more efficacious than the polyvalent streptococcic vaccine and various other agents by which a febrile reaction can be produced, such as antistreptococcic serum, milk and horse serum. These observations suggest that the typhoid vaccine does not act solely by producing a febrile reaction, but that it may have some specific action on chorea. The conclusions are that: 1. The best clinical results in the treatment of chorea have been observed in the presence of a severe febrile reaction, either on a toxic or an infectious basis. 2. The most spectacular results are observed in the course of a superimposed or parallel infection. 3. Typhoid vaccine may have a specific action on chorea.

BODER, Chicago.

Diseases of the Ear, Nose and Throat

A STUDY OF THE SINUSES AND SINUSITIS IN INFANTS AND CHILDREN. CHARLES GILMORE KERLEY and EDWARD J. LORENZE JR., M. J. & Rec. **139**:213 (March 7) 1934.

In this study six hundred and seventy roentgenograms were taken, twenty-three of which were of new-born infants. Sinus disease in the child from a diagnostic point of view is different from that of the adult. The explanation of this is given. The authors paid special attention to the roentgenographic appearance of the normal sinuses at different ages of infancy and childhood, at what period of life the sinuses may be roentgenographically demonstrated, the roentgenographic appearance in sinus disease and the relation of sinusitis in children to bodily ailments. Among the patients under observation, 337 males and 310 females showed

sinus disease. The location of the sinusitis and the disorders for which the children were under observation are enumerated. The management of the cases is described, and many roentgenograms of normal and diseased sinuses are presented.

WILLIAMSON, New Orleans.

DEAFNESS IN NASSAU COUNTY SCHOOL CHILDREN. GERARD H. COX, M. J. & Rec. **138**:452 (Dec. 20) 1933.

Seven hundred and forty-nine pupils were examined. Thirty-eight, or 5.07 per cent, were found to have defective hearing. Twenty-three, or 3.007 per cent, had unilateral deafness, and fifteen, or 2 per cent, had bilateral deafness. Fowler's procedure for making the tests on the children is given verbatim in the article. Tubal catarrh and chronic catarrhal otitis media, associated with hypertrophied tonsils and adenoids, accounted for the largest group of those hard of hearing.

The author's statistics show the importance of employing this test routinely in the public schools at least once a year, in order that pupils with mild grades of defective hearing may be identified and treated while the disease is in the incipient stage.

WILLIAMSON, New Orleans.

CHRONIC SUPPURATIVE OTITIS MEDIA (OBSERVATIONS REGARDING ITS PREVENTION; THE EXAMINATION AND TREATMENT) JESSE W. DOWNEY JR., West Virginia M. J. **30**:97 (March) 1934.

Each case of chronic suppurative otitis media requires painstaking examination, careful classification and individual treatment.

Marked progress has been made in the prevention of this condition. Endeavors to build up the general resistance of susceptible children, and careful and well thought out nasal treatments and operations undoubtedly reduce the number of attacks. Prompt and proper incision of the drum head in upper respiratory infections in children, especially in scarlatina, measles and influenza, has become a routine of inestimable value. Persistent purulent discharge after other symptoms have subsided is an indication for simple mastoidectomy in selected cases. Chronic discharge may continue for years without discomfort beyond the annoyance of the discharge, but it is a constant source of great danger of serious developments.

The author outlines his method of examination and presents the points that should be developed in the taking of histories and in examination.

This is an extensive and valuable article. SHAWKEY, Charleston, W. Va.

ROENTGENOLOGIC OBSERVATIONS OF THE SKULL AND LARYNX OF DEAF-MUTES. J. DILLON, B. PREOBRASCHENSKY, S. WULFSON and G. FOMIN, Ztschr. f. Hals-, Nasen- u. Ohrenh. **5**:219 (Feb. 10) 1934.

Dillon and his co-workers studied the skulls and larynges of sixty deaf-mute children by roentgenography in an attempt to determine whether there were any typical anatomic characteristics. The children ranged in age from 9 to 17. There were twenty-five boys and thirty-five girls, who were divided into groups. The first consisted of thirty-nine children with inborn deaf-mutism; the second, of sixteen with acquired deaf-mutism but without visible otoscopic changes, and the third, of five with acquired deaf-mutism and with otoscopically demonstrable destructive changes in the middle or outer ear or the mastoid process. Special reference was made to the synosteosis of the cranial sutures. It was found that the coronal sutures were missing in 36.8 per cent of group 1 and in 30 per cent of groups 2 and 3. The authors conclude that in cases in which the bone is influenced by increased osteogenesis, an increased pressure is exerted on the growing brain which can produce a deformity of the skull. What is the relationship of these observations to deaf-mutism the authors do not know, but they believe that the process exerts an unfavorable effect on the further development of deaf-

mutism. With regard to the pneumatization of the temporal bone, it was found that except for the third group, who presented a condition in which mastoid sclerosis is usually found, there was no essential difference from the normal. Roentgenography of the larynx was carried out by taking the picture from the side in such a way that the two halves would coincide when the films were developed. For this purpose the patients were divided into three groups according to age, i. e., 9 to 12, 13 to 15 and 16 to 18. The authors conclude that there is at first too little use and later too much use of the larynx. This may be the origin of the early wear and tear of the larynx but is based on an unfavorable constitutional predisposition.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

Diseases of the Skin

MULTIPLE HEMANGIOMAS IN AN INFANT. A. C. TAYLOR and E. MOORE, Am. J. Cancer **19**:31, 1933.

In an infant multiple hemangioma involved the skin, liver and lungs. The question of metastasis is discussed, but no definite conclusions are reached.

[ARCH. PATH.]

HEREDITARY ECTODERMAL DYSPLASIA OF THE ANHIDROTIC TYPE; REPORT OF A CASE, WITH THE RESULTS OF BIOPSY. A. M. HILL, Arch. Dermat. & Syph. **28**:66 (July) 1933.

Hill reports the case of a boy, 6⅓ years old, in whom sweat glands were completely absent, as was shown by biopsy of tissue from the axilla. He had also very fine, scanty hair, and his teeth consisted of two widely separated cone-shaped teeth in the region of the upper incisors and one upper right molar; there were no teeth in the lower jaw. The hereditary factor was traced through the maternal grandmother and mother and was also found in the patient's two sisters. The dental defect was noted in all these, and the two sisters also had very scanty hair. The mother gave the history of perspiring little before puberty, but she seemed normal at the time of writing. The author thinks that this condition is more common than a review of the literature would indicate.

DULIN, Iowa City.

HEREDITARY CANITIES AND VITILIGO. LESTER HOLLANDER and CHARLES L. SCHMITT, Arch. Dermat. & Syph. **28**:697 (Nov.) 1933.

The authors show photographs of the father and his two daughters, in whom the location of the canities was the same. The vitiliginous areas on the bodies of the sisters corresponded closely. The hereditary tendency of this anomaly of pigmentation is again brought out.

DULIN, Iowa City.

CONTACT ECZEMA; RUBBER CEMENTS AS ADHESIVE IN PATCH TESTING. BEDFORD SHELMIRE, Arch. Dermat. & Syph. **28**:795 (Dec.) 1933.

Because of the large number of patients who react to adhesive tape, a substitute in patch testing was sought. The author found "Frisket" liquid rubber cement especially applicable. This he had placed in a metal tube for ointment with a screw-cap by a local druggist. When the contact tests were applied to a large number of patients, none reacted by local dermatitis, although many of these were sensitive to adhesive tape.

DULIN, Iowa City.

ACRODYNIA. I. J. WOLF and CHARLES DAVISON, J. Pediat. **4**:498 (April) 1934.

The observations at autopsy in a case of acrodynia in a 2 year old boy are reported in detail. There were marked swelling of the ganglion cells of the

third cortical lamina, the large ganglion cells of the neostriatum and the Purkinje cells of the cerebellum and severe pathologic changes in the nerve cells of the locus caeruleus and the cervical portion of the spinal cord. The changes in the peripheral nerves were similar to those seen in peripheral neuritis.

LEMASTER, Evanston, Ill.

TREATMENT OF ECZEMA. F. GIERTHMÜHLEN, München. med. Wchnschr. **80**:1398 (Sept. 8) 1933.

True eczema occurs mostly in children between 3 and 18 months of age. Most observers consider it an allergic manifestation, usually a food allergy. For proper treatment the quantitative and qualitative make-up of the diet must be considered. Overfeeding should be avoided. Changing the diet from whole milk to buttermilk or skimmed lactic acid milk is often effective. If the eczema does not improve, other allergic factors, such as eggs, flour and the milk, must be considered. Goat's milk may be substituted for cow's milk. Vegetables and fruit juices should be added to the diet at an early age. Undernourished children may require a diet high in calories. In older children eczema is often of nervous origin and frequently improves when a vegetarian diet is given. Local treatment with ointments and powders is helpful.

BRAHDY, Mount Vernon, N. Y.

THE MECHANISM OF THE URTICARIAL IDIOSYNCRASY TO EGG WHITE IN THE ECZEMATOUS CHILD. WERNER JADASSOHN and FRITZ SCHAAF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:407, 1933.

Dialysates of egg white are known to be urticariogenic in the allergic eczematous child. Opinions differ as to whether the reacting substance is of protein nature, or, as Jadassohn and Schaaf and others maintain, a nonprotein substance. When the proper technic is employed, no protein substances pass into the dialysate. An analysis of the reports to the contrary discloses faults in the technic of dialyzing or in the methods of determining the presence of protein substances in the dialysates. The comparison, by means of the Prausnitz-Küstner technic, of the urticariogenic potency of egg white and of dialysate revealed that the latter reacted in quantities which could not contain the minimum concentration of protein found necessary in quantitative tests with egg white. By means of the Prausnitz-Küstner technic it was possible to demonstrate that chicken egg white contains at least two antigenic substances; one of them is also present in duck egg white. Both pass through the dialyzing membrane. The blood serum of eczematous children with urticarial hypersensitiveness to egg white contains substances which can neutralize the urticariogenic properties of egg white. By means of the Schultz-Dale technic trichophytin produced anaphylactic phenomena in dilutions which made it probable that that reaction was not due to protein substances. Jadassohn and Schaaf conclude that urticarial hypersensitiveness and anaphylaxis are closely related.

I. DAVIDSOHN. [ARCH. PATH.]

Surgery and Orthopedics

CLINICAL AND THERAPEUTIC COMMENTS ON SARCOCOXITIS. RICHARD, DELAHAYE and J. CALVET, Rev. d'orthop. **20**:97 (March-April) 1933.

In children and in adults alike the initial lesion is in the bone, and the articular invasion is secondary. In children the osteitis, which generally appears in the ilium, originates remote from the articulation. For a considerable period the clinical and roentgenologic signs are those of simple osteitis, and the lesion may heal without reaching the epiphyseal line. Articular involvement is rare; it is always delayed, and may be partial or severe. Patients frequently apply for treatment only when an abscess forms. Roentgenograms show, parallel to the posterior border of the wing of the ilium, an elongated cavity with or without a

sequestrum at some distance from the epiphyseal line and bounded in front by a border which cannot be recalcified. The upper border ends in a culdesac before reaching the iliac crest; at the lower border there is erosion of the edge of the sciatic notch. The wing of the ilium always presents a marked disturbance of growth. Focusing the roentgen ray normally on the center of the pelvic cavity does not show the exact relation of the osteitis to the articulation as well as focusing on the sacro-iliac angle, the plate being exposed while the child is turned away from the affected side. The roentgenologic signs are the sacro-iliac diastasis and the separation at the pubis. At first roentgenography often reveals nothing, but the presence of a diastasis, either partial or total, removes all doubt. Separation may appear early, and in that case it indicates torsion of the iliac bone on the sacrum from muscular imbalance between the rectus abdominis and the sacrolumbar muscles. Prolonged repose will diminish this imbalance. Delayed pubic separation is due to raising of the iliac bone by destructive pseudarthrosis.

VINTON, Brooklyn.

CLINICOROENTGENOLOGIC STUDY OF VESICAL CALCULOSIS IN CHILDREN. MARIA PELLINI, Pediatria **42**:1 (Jan. 1) 1934.

Two cases of calculosis of the bladder are reported. In the first, that of a child 4 years old, clinical diagnosis was confirmed by roentgen examination. In the second, that of a baby 15 months old, clinical symptoms were nearly absent, and the diagnosis could be stated early only through roentgen examination. Cystotomy and removal of the stone were performed; prompt healing followed.

A comparative analysis of the studies by other authors on this subject, especially in regard to the etiology, symptoms and differential diagnosis, and of his own cases, led the author to the following conclusions: 1. Calculosis of the bladder in infants is more frequent than has heretofore been suspected. 2. Early diagnosis through clinical observations only is difficult, and therefore urinalysis, rectal exploration, cystoscopy and roentgen examination are always necessary. Roentgen examination is of the greatest value, but this value must not be overrated, as a great number of stones in infants may be transparent to the roentgen rays, in which case a negative finding would not exclude a diagnosis of calculosis. 3. Even a positive finding must be cautiously considered, as a few diseases of the urinary tract and extra-urinary organs may simulate this condition.

The article closes with a brief review of the course, complications, pathology, pathogenesis and therapy in these cases.

SIGNORELLI, New Orleans.

Miscellaneous

TWINS AS BIOLOGIC CONTROLS IN THE STUDY OF HUMAN CONSTITUTION. H. M. MARGOLIS and V. W. EISENSTEIN, Ann. Int. Med. **6**:1489 (May) 1933.

This report deals with a study of identical twins reported in the literature in an endeavor to answer the question: If a person is by constitution a candidate for a specific disease, would the same disease develop in another trial of life? In the material collected from the literature many cases are described in which the same disease attacked both identical twins simultaneously but under conditions that would indicate the rôle of a latent constitutional susceptibility.

READING, Galveston, Texas.

ULTRA-VIOLET ENERGY: ITS EFFECT AND INTENSITY AT VARIOUS LOCATIONS AND ALTITUDES. M. K. WILDER, ROBERT S. ROCKWOOD and SAMUEL B. LIPPINCOTT, Ann. Int. Med. **7**:605 (Nov.) 1933.

This article stresses the fact that in high altitudes in arid and semi-arid regions the percentage of short waves reaching the earth's surface is much higher than in low altitudes, where the humidity is greater and where, with the increased density

of population, there is a greater amount of smoke and dust in the atmosphere, which further reduces the number of short waves reaching the earth's surface.

READING, Galveston, Texas.

THE RELATIONSHIP OF SEX TO DISEASE. EDGAR V. ALLEN, Ann. Int. Med. **7**:1000 (Feb.) 1934.

In this interesting study the author has considered only diseases which affect structures common to both sexes. Diseases of the digestive tract, respiratory tract, blood, blood vessels, heart, bones, joints and urinary tract, functional nervous diseases and miscellaneous diseases are studied from the standpoint of both morbidity and mortality. From the former point of view it would appear that females are ill more than males, but that in the male there is a higher incidence of most diseases which might permanently endanger health or life. When mortality is considered, the rate is higher among males, except in persons between the ages of from 20 to 34 years, inclusively, when the mortality rate is higher in females, apparently due to the mortality resulting from childbirth.

That the higher mortality in males is not explainable on the basis of habits peculiar to the male is evidenced by the fact that there is a higher mortality for males during intra-uterine life and for the first five years of extra-uterine life, as well as by the fact of the predominance of congenital deformities in males.

The theory is advanced that the male, representing advanced or more specialized development, is more susceptible to disease. Whatever the explanation for the influence of sex on disease may be, it appears incontrovertible that a sex-linked inferiority of the male exists; that mere maleness influences unfavorably the resistance of the organism to disease during all ages, and thus the price of maleness is weakness. How ironical, therefore, seems the precept of the apostle I Peter: 1:13: "Give honor unto the wife or unto the weaker vessel."

READING, Galveston, Texas.

INFANT HYGIENE FOR MOTHERS. A. B. MARFAN, Nourrisson **21**:301 (Sept.) 1933.

Marfan believes that it is important that appropriate courses in infant hygiene be given by pediatricians. A proposed course with subjects for twenty-five lectures is outlined. These should be given preferably at a babies' hospital or clinic where sick and well infants can be used for demonstration.

MCCLELLAND, Cleveland.

CHILD WELFARE WORK IN PERU. L. A. SUARES and F. CHUECA, Bol. Inst. internac. am. de protec. a la infancia **7**:191 (Oct.) 1933.

The authors studied the conditions of the Peruvian child and found that among 1,242 children of the popular classes, 54 per cent were of a weight lower than normal. Among the same children, those aged between 1 and 2 years were in more unfavorable conditions, for 72 per cent of these were under normal weight. Almost the same was found as to the children's height, although the percentage was smaller; only 29 per cent of the children were under normal height.

As a natural consequence of such conditions the infant mortality is high, though it has been decreasing, according to the figures furnished by the city of Lima. In 1924, when the population of this city was 186,657, the mortality for infants under 1 year of age was 8.4 per thousand inhabitants, 21.5 per hundred births and 34.2 per hundred deaths. In 1932, when the city had 278,733 inhabitants, the figures descended to 4.9, 15.8 and 24.2, respectively.

Ignorance and poverty of the parents are the principal causes of the children's physical misery; these factors lie at the bottom of their inadequate feeding and the want of bodily and housing cleanliness and are responsible for the propagating of venereal disease, tuberculosis and other diseases.

State interference in the child welfare work became more efficient through the creation of the Board for the Defense of Childhood in 1932 and, later, of the

National Child Institute, a technical organization with a wide range of action through its prenatal and postnatal services in the infants' dispensaries and *gouttes-de-lait,* etc., for children under 2 years of age; its day service in the *crèches* for children under 4 years of age, and its altitude colonies for children between 6 and 15 years of age. The total number of children assisted in 1932 was 11,249, 193 of whom were boarders in the altitude colonies.

The social service carried out in the different divisions of the Institute promotes the divulgation of rules regarding child health, which the mothers must learn and practice. On the other hand, the Institute, assisting the child from its birth, is in the most favorable condition to apply vaccination with B C G.

AUTHORS' SUMMARY.

EFFECT OF CAMPING ON YOUTH. KAREL HORA, Thomayer Collection of Monographs, no. 167, supp., Časop. lék. česk., Aug. 26, 1932.

Hora examined forty-three boy scouts before and after a month of camping during which rest, hygiene, calisthenics, light work and five light meals in twenty-four hours were the regimen. More than two thirds of the boys gained in weight, height, strength of muscle, circumference of forearm, vital (lung) capacity, circumference of chest after inspiration and Spehn and Matiega indexes, i. e., $C \times P/S$ and $C \times S/P$, respectively, in which S equals height, P equals weight and C equals vital capacity. Limitation of activity was imposed only in a few instances in which the boys showed a slight loss.

STULIK, Chicago.

EXPERIMENTAL STUDY OF THE THYROID FUNCTION DURING PREGNANCY, PARTURITION AND PUERPERIUM. U. NAKAMURA, Jap. J. Obst. & Gynec. **16**:244 (June) 1933.

By using the Baumann-Anten method of measuring iodine, Nakamura has observed the thyroid function in the rabbit during pregnancy. The lobes of the thyroid are equal to each other in weight and seem to contain an equal quantity of iodine. After extirpation of one lobe, the remaining lobe increases in size and produces more iodine than usual. However, the quantity of iodine found in the lobe is smaller in proportion than the increase in weight of the remaining lobe. On the other hand, during the puerperium, the quantity of iodine increases while the size of the remaining lobe remains constant. This difference in the quantity of iodine is explained by the hyperfunction of the thyroid gland during pregnancy leading to a secretion of iodine into the blood stream, while in the puerperium there is a period of depression which brings about an accumulation of iodine in the gland itself.

ADAIR and TESAURO, Chicago.

MORTALITY AMONG INDO-EUROPEAN INFANTS IN THE DUTCH EAST INDIES BETWEEN 1929 AND 1931. J. D. DE HAAS, Maandschr. v. kindergeneesk. **3**:1 (Oct.) 1933.

The mortality of infants among the Indo-European children in the Netherland Indies between 1929 and 1931 was 6.9 per cent, with a birth rate of 26.3 per thousand. For such a well-to-do population this mortality is rather high, especially as severe rickets does not occur in the Indies. The mortality among the boys was higher than that among the girls. The highest mortality was on the Molukka Islands (14 per cent); the lowest, in the eastern part of Sumatra (3.1 per cent), where the hygienic and material conditions of the Europeans during the years mentioned were excellent. The mortality was highest in January. (The beginning of the rainy season was marked by an important increase in the mortality, probably caused by an increase of cases of pneumonia.) Tropical heat has no definitely unfavorable influence on these European children.

VAN CREVELD, Amsterdam, the Netherlands.

Society Transactions

SOCIETY FOR PEDIATRIC RESEARCH

Annual Meeting, May 1, 1934

RUSTIN MCINTOSH, M.D., *President, in the Chair*

PERMEABILITY OF THE ERYTHROCYTES OF DOGS AND MONKEYS IN VIVO. DR. DANIEL C. DARROW and DR. HERMAN YANNET, New Haven, Conn.

Data are presented describing the equilibration of the erythrocyte of the dog and monkey in changing concentrations of extracellular electrolyte, particularly, sodium, chloride and bicarbonate. In the monkey, the red cell of which contains potassium as the preponderant cation, reducing or increasing the serum electrolytes produces changes in volume in the red cells resulting from shifts in water. However, no evidence of permeability to the serum cations could be demonstrated. In the dog, the red cell of which contains sodium as the principal cation, similar procedures produce not only changes in volume but also definite evidence of shift of sodium into and out of the red cells.

DISCUSSION

DR. G. M. GUEST, Cincinnati: In such studies as these a balance of the chemical constituents of the blood cells in terms of their acid and base equivalents cannot be reckoned closely without consideration of the organic phosphoric acid compounds of the cells. There is good evidence that these compounds behave as acids, binding approximately one molecular equivalent of alkali per mol of phosphoric acid. The fraction designated ester-P especially merits attention, as it is fairly labile and its concentration in the cells has been found to vary considerably in response to different chemical changes in the body. It seems likely that the excess of determined bases over the determined acids in the blood cells, as noted in the experiments presented by Dr. Yannet, may be accounted for in considerable part by the undetermined organic phosphoric acid compounds.

DR. DANIEL C. DARROW, New Haven, Conn.: It is difficult to explain the equilibrium between the electrolyte of the cells and that of the serum in the experiments in which the level of cell sodium has been raised but has not returned to normal a week later. Under these circumstances the electrolyte of the serum is normal, yet the electrolyte of the cell is still high. The water content of the cell is normal, since the cell protein is normal. If one assumes that the excess sodium is bound to phosphates, these salts would probably be dissociated and osmotically active. We are inclined to assume a change in cell p_H, which increases the amount of base bound by hemoglobin. The base bound to hemoglobin is probably not so highly dissociated as that bound to phosphate. It is not easy to explain the osmotic equilibrium between cells and plasma under these circumstances.

METABOLISM OF IRON AND RELATED MINERALS. DR. LOUIS K. DIAMOND, Boston.

During the investigation of the problem of absorption and utilization of iron, experiments *in vitro* tended to show that the dialysis of iron was interfered with by the presence of phosphate salts in the solution. To test the possible interfering effect of each of these elements (iron and phosphorus) on the other in absorption from the intestinal tract, young rats were fed standard diets relatively high in calcium and low in phosphorus. The control diet was nonrachitogenic. The Steenbock diet was constantly rachitogenic. The control diet, to which iron in the form of ferric chloride was added, produced constantly changes qualitatively

similar to those produced by the standard rachitogenic diet but quantitatively more severe. The criteria for judging this were the marked lowering of the blood phosphorus in the experimental animals, the typical changes in the roentgenograms and the characteristic changes seen in the sections of the long bones when microscopically studied.

Other salts of iron were added to the control diet and tested in the same way; when added in comparable amounts they produced similar rachitogenic changes. The salts so tested were ferrous chloride, ferric ammonium citrate and reduced iron. The addition of viosterol to the ferric chloride diet was shown to protect the animals from the development of rickets. Likewise, the addition of viosterol to the diet after the development of rickets on the iron-containing diet caused rapid healing of the rachitogenic process. The addition of excess phosphorus to the iron-containing diet also protected the animals from the development of rickets.

Since certain other minerals related to iron have been thought to have an important bearing on the absorption of iron from the intestinal tract, it was considered advisable to test each of these as supplements to the control diet. Accordingly, manganese, zinc, aluminum, cobalt and copper were each added. Cobalt and copper were toxic and killed the animals within four days. Manganese, zinc and aluminum produced changes typical of rickets in every respect. Likewise, the addition of viosterol to each of these diets protected against the development of rickets.

In speculating briefly on the mechanism of the production of rickets by these various metals, simple interference with absorption was suggested; that is, iron or the other metals tried might enter into chemical combination with the phosphorus of the diet in the intestinal tract and prevent absorption of this element so as to produce typical low-phosphorus rickets. Proof of this simple theory is lacking at present.

It was emphasized that an important implication of these experiments was the possible interference of phosphorus with the absorption of iron from the intestinal tract, especially in the use of this element in the treatment of hypochromic anemia. Preliminary investigations seemed to support this possibility and suggested the need for further study of this factor in the metabolism of iron.

DISCUSSION

DR. HUGH W. JOSEPHS, Baltimore: I should like to know whether any balance experiments were done on the rats. It is hard to believe that absorption from the intestines alone was responsible for the rickets. I should think that it would be necessary to carry out control tests to prove that point.

DR. CARL H. SMITH, New York: Dr. Diamond's results have a practical bearing. In a group of about thirty-five infants who were followed in the outpatient department of the New York Hospital, from 30 to 50 grains (1.9 to 3.2 Gm.) of iron was administered daily in order to study the effect on the development of anemia. Of course, this was always supplemented with viosterol. In one infant the iron was increased to the maximum quantity, while the dose of viosterol remained unchanged—10 drops a day. At the next visit, one month later, florid rickets was observed.

DR. BENJAMIN KRAMER, Brooklyn: The rickets produced by iron in this rachitogenic diet is different from that produced by strontium. Apparently, rickets produced by iron under the administration of vitamin D is curable. In rickets produced by strontium that is not the case. If one attempts to cure rickets caused by strontium with vitamin D, one can give large quantities of the vitamin without affecting the condition. Furthermore, in rickets due to strontium it is impossible to produce any calcification *in vitro*, even when using solutions containing calcium and inorganic phosphorus with a product of 60 and sometimes even higher, so that strontium seems to have some specific local effect on the cartilaginous matrix and the calcifying osteoid, whereas iron acts chiefly by interfering with the absorption of phosphorus from the gastro-intestinal tract.

DR. A. T. SHOHL, Boston: The question of the effect of vitamin D in this case illustrates that this diet is effective. The metabolism of iron may not necessarily determine the absorption of calcium, phosphorus or iron, but may depend on the condition of the body after the material has been absorbed. I think that many of the salts are absorbed and used effectively in the body. It is not necessary to prove that lack of solubility means lack of absorption or utilization.

I should like to raise one point with regard to the experiment which Dr. Hamilton reported last year—the possibility of using sodium instead of ammonium chloride, because of the effect of chloride on the acid base.

DR. LOUIS K. DIAMOND, Boston: Some interesting work is being done by Brock, who is studying the balance of animals and human beings fed on iron. He recently wrote me that he is having difficulty in trying to prove that rickets caused by phosphorus is due to the amount of absorption of other mediums. I purposely omitted mention of rickets due to strontium. This type of rickets is not the same as other types and is not affected by vitamin D.

As to the practical application, it is believed that ordinarily the diet of human beings is sufficiently rich in phosphorus, and the amount of iron added, even in large doses of medicinal iron, is comparatively small, so that the production of a rachitogenic effect with large amounts of iron is unlikely. The doses of iron given to the animals studied were to human beings from ten to twenty times as great as those given in severe anemias. But it is possible that with the minimum amount of phosphorus and large amounts of iron and without vitamin D one would get a rachitogenic effect.

One theory which still demands investigation for proof is that iron, when used in its most soluble form, should be given in mediums containing large amounts of phosphorus and should be used with vitamin D, if possible, at the same time. We have at least a dozen patients at present who have been fed a minimum amount of iron in various diluents, some containing large amounts of phosphorus and some not, and some containing viosterol and some not; there seems to be a definite effect in that patients who receive those containing much phosphorus and no vitamin D show less improvement than patients who receive those containing no phosphorus and vitamin D.

THE USE OF LYOPHILE HUMAN SERUMS FOR PREVENTION AND TREATMENT IN INFECTIOUS DISEASES. DR. JOSEPH STOKES JR., DR. STUART MUDD, DR. R. L. RODDY, DR. HARRY EAGLE, DR. E. W. FLOSDORF and DR. P. LUCCHESI, Philadelphia.

The development of a sterile, dry, readily soluble serum in which the antibodies are preserved intact has been the culmination of experiments dating from the original studies of Ehrlich. Martin, in 1895, and Shackell, in 1909, were responsible for the major advances previous to the recent developments of the method by Elser, Reichel, Flosdorf and Mudd.

The method is essentially distillation in a vacuum. The sterile blood serum is placed in small glass containers and frozen at —74 C. in a bath of carbon-dioxide ice and acetone. The containers are attached by glass tubes to an already partially evacuated manifold, which in turn is connected to oil vacuum pumps. At some distance from the manifold and in the vacuum line is placed a large condenser bathed in carbon-dioxide ice and acetone. Once the serum is frozen it remains so during the entire evacuation of the water. The bulk of the serum changes little, remaining a light, porous, readily soluble powder and containing approximately 0.1 per cent of its original water. The glass tube attached to the small containers is sealed by flame, and a vacuum is thus maintained which assists in maintaining sterility and also enhances the ready solubility of the lyophile serum in distilled water injected through a rubber stopper at one end of the container. The serum is readily dissolved in much smaller amounts of water than it originally contained, and when injected intramuscularly in solutions four times concentrated is also readily absorbed.

The complement in guinea-pig lyophile serum has remained unaltered over a period of four months at icebox temperatures. Many of the ordinary commercial antibacterial and antitoxic serums have been processed, without any evidence of alteration in the titer of the antibody.

Pooled adult serum and convalescent measles serum were processed and injected into one hundred and twenty-nine children who had been exposed to measles. Most of these contacts were in the home, and the patients were treated by the family physician. Of these children, sixty-six showed an attenuated form of measles, which was usually desired by the physicians; sixty-three were completely protected, while three, who had received lyophile serum from a single adult, showed typical cases of measles. Three moderate local and general reactions were noted, with local pain and swelling and fever lasting more than from twenty-four to thirty-six hours. All these reactions were caused by a single small quantity of processed serum, so far as could be determined.

Convalescent mumps lyophile serum was injected intramuscularly into seven children who had been intimately exposed to mumps on a hospital ward, and no cases developed. Convalescent chickenpox lyophile serum was injected intramuscularly into twenty-three children who had been intimately exposed to chickenpox on a hospital ward; in these also no cases developed. Convalescent scarlet fever lyophile serum was injected intramuscularly into seven children who had been exposed to scarlet fever, and no cases developed. Dick tests were not performed previous to the injection. This serum was also used intramuscularly in two cases of severe scarlet fever, and marked improvement was noted in both.

DISCUSSION

DR. J. D. TRASK, New Haven, Conn.: Did Dr. Stokes make any studies of the antigenic properties of the lyophile serum? For example, was it apt to produce active sensitization in the guinea-pig?

DR. STUART MUDD, Philadelphia: The specimens of serum which Dr. Stokes has passed around have had only a third and a fourth of their original volumes of water added to them. They are not perfectly dissolved. Such concentrated serum, however, is well absorbed after intramuscular injection. Human serum, even when regenerated with its original volume of water, may be turbid, probably due to its lipoids. We do not recommend the intravenous administration of lyophile human serum pending further testing.

May I speak briefly of an aspect of the work which I think Dr. Stokes intended to mention, namely, the Philadelphia Serum Exchange? Despite the growing recognition of the prophylactic and even therapeutic value of pooled adult or convalescent human serum in certain conditions, it is still customary to wait until an emergency has occurred before taking steps to secure such serum. In a few cities, however, the effort has been made to render secure a supply in advance of the emergency for which it is needed. Thus, in Paris (Tzanck, A.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:341, 1933) and in Detroit (Gordon, J. E.: *J. A. M. A.* **100**:102 [Jan. 14] 1933) convalescent or vaccinated donors are on call for transfusions or as sources of serum.

The method of drying serum from the frozen state is making possible its preservation, apparently for an indefinite period. It thus becomes possible to collect convalescent serum or normal adult serum when it is available and to hold it for use when needed. To realize these advantages, the Children's Hospital of Philadelphia has established a Serum Exchange to receive and dispense adult and convalescent serums. The serums are preserved in lyophile form. They are made available to physicians as need arises for prevention or treatment in diseases such as measles and scarlet fever, in which they are of recognized value. The serums are being subjected to clinical test in conditions such as typhoid fever and staphylococcic infections, in which there are indications of usefulness but in which further clinical trial is needed.

DR. E. A. PARK, Baltimore: Has convalescent serum been successfully concentrated and preserved in this fashion? I should like to point out that the collec-

tion and preservation of blood from those who can spare it, with a view to its distribution among those who require it, marks a socialistic movement in medicine.

DR. E. W. FLOSDORF, Philadelphia: I might add another point from the chemical side. So far as we have been able to determine, the proteins do not have their properties changed in any way as a result of the process. Their properties are completely retained after re-solution of the material. Of course, if there are any lipoids present in the serum before it is processed, due to a recent meal before bleeding, re-solution of that serum will not result in the redispersion of the lipoids present, since they are not lyophile. If the serum is not too lipemic and is properly prepared, after re-solution it will appear the same as the original, and its chemical properties will be practically identical with those of the original.

DR. JOSEPH STOKES, Philadelphia: Concerning Dr. Park's question, we have not been satisfied to use the lyophile serum intravenously in cases of nephrosis until such attempts have been made first in experimental animals with processed homologous serum.

DR. HARRY EAGLE, Philadelphia: The antigenic properties of proteins are not affected by the process.

AN EXPERIMENTAL APPROACH TO POSTINFECTION ENCEPHALITIS. DR. FRANCIS F. SCHWENTKER, New York.

Fresh rabbit brain injected into rabbits fails to cause the formation of antibodies capable of reacting in complement-fixation tests with either aqueous emulsions or alcoholic extracts of rabbit brain. Such antibodies are produced, however, after the injection of (1) fresh rabbit brain to which a foreign protein, viz., pig serum has been added, (2) sterile rabbit brain which has been allowed to autolyze by standing at room temperature, or (3) brains of rabbits ill with encephalitis caused by a vaccine virus. The antibodies thus produced have been shown by experiments in absorption to be made up of an organ-specific but not species-specific brain antibody and a nonspecific element which reacts weakly with various organs. The specific brain antigen is an alcohol-soluble lipoid, which is present in greater amounts in the white matter than in the gray matter. Although it is absent in the brains of fetal rabbits, it increases with age to a maximum at maturity. This indicates that the antigen may be myelin. It is suggested that a further field for investigation is offered in regard to the possible relation between this antibody and postinfection encephalitis.

DISCUSSION

DR. BENGT HAMILTON, Chicago: I should like to ask Dr. Schwentker whether the destruction of brain by other agencies, in infections, vascular accidents, tumors and so on, would not be followed by the same results as in virus disease.

DR. FRANCIS F. SCHWENTKER, New York: I have carried out no studies along the lines that Dr. Hamilton has just mentioned, but an article published in England states that in cases of injury to the brain due to fractures or wounds sustained during the war in which the patient died from ten to twenty days after the injury there were certain changes in the brain substance which were not believed to be due to injury of this kind, but no attempts were made to study what the antibody content of the serum was in such cases.

PROTECTIVE INOCULATION AGAINST TUBERCULOSIS IN INFANTS BY THE USE OF HEAT-KILLED HUMAN TUBERCLE BACILLI. DR. T. CAMPBELL GOODWIN and DR. FRANCIS F. SCHWENTKER, New York.

The vaccine used in this work was prepared from a virulent strain of human tubercle bacilli. Seventy-three young infants who had not been exposed to tuberculosis were given from 36,000,000 to 120,000,000 heat-killed bacilli intramuscularly. All but one of these children showed a positive reaction to the Mantoux test within from three to twelve weeks. No constitutional reaction to the administration of

the vaccine was noted, but in sixteen children sterile abscesses developed at the site of inoculation. These were small and disappeared quickly.

The inoculated babies were examined at frequent intervals; tuberculin tests were done, and many roentgenograms of the lungs were taken. Of fifty vaccinated infants who were followed for more than a year, one died of tuberculosis; one had clinically demonstrable tuberculous infection, and sixteen showed roentgen shadows which could be interpreted as enlargement of the hilar lymph glands.

It was impossible to establish an accurate control group, but in the nearest approach we could find to such a group both the mortality and the morbidity were higher than in the inoculated children.

We believe that the method is a hopeful one, and we have the clinical impression that the intramuscular injection of heat-killed human tubercle bacilli affords some degree of protection against tuberculosis to young infants. Because of the low mortality rate—our only criterion of the efficacy of the vaccine—it will be necessary to study a larger group over a long period of time before accurately evaluating this method.

DISCUSSION

DR. HARRY EAGLE, Philadelphia: I should like to ask whether any of the inoculated children received a second injection and if so whether there was any difference in the response.

DR. RUSTIN MCINTOSH, New York: I should like to ask Dr. Goodwin whether he observed any rise of temperature at about the time of the development of the allergy comparable to the initial fever of the primary infection in tuberculosis.

DR. T. CAMPBELL GOODWIN, New York: We did not inoculate twice. It has been found in animals that the original focus of tuberculosis may flare up when dead tubercle bacilli are injected.

EFFECT OF DIETS HIGH AND LOW IN CHOLESTEROL ON RESISTANCE TO PARATYPHOID INFECTION IN RATS. DR. WARREN M. SPERRY and DR. V. A. STOYANOFF, New York.

On the basis of relatively few experiments, several authors have concluded that feeding animals with cholesterol increases resistance to bacterial infection. In the present investigation this important conclusion has been subjected to further test. Rats were paired at weaning according to sex and, in most instances, according to litter. One member of each pair was placed on a diet containing practically no cholesterol; the other rat received the same diet, except for the addition of 1 or 2 per cent of cholesterol. After a considerable time on these diets both rats were given an injection of the same dose of a culture of Salmonella Danysz, and the period of survival was noted. Except in a small preliminary series which was complicated by probable vitamin G deficiency, no evidence was obtained of any effect of dietary cholesterol on resistance to this paratyphoid organism. Our experiments, of course, give no information concerning the effect of the feeding of cholesterol on other infections, but at least they indicate that cholesterol does not exert a general protective action.

ORIGIN OF LACTOBACILLUS BIFIDUS AND ITS POSSIBLE RELATION TO CELIAC DISEASE. DR. HATTIE E. ALEXANDER, New York.

In 1908, Herter reported that the intestinal flora of patients with celiac disease was abnormal, because it showed persistence of the flora found in the new-born nursling. This is characterized by marked predominance of Lactobacillus bifidus. While it was not thought that this flora was the etiologic agent, it was hoped that it might be of value in diagnosis, if it could be found in all cases of celiac disease, with negative results in a control group. Eight cases of celiac disease were studied, and Lactobacillus bifidus was isolated in large numbers in every case. The method consisted in obtaining anaerobic cultures of saline dilutions of suspensions of stools on liver dextrose lactose agar. After a short period of a strict celiac

diet, Lactobacillus bifidus showed a striking decrease and often complete disappearance from the stools of these children. A similar investigation of twenty-two controls yielded results which indicated that if normal children of the celiac group are followed over a sufficiently long period Lactobacillus bifidus can be isolated in a large percentage of cases, but there is great variation in the numbers of colonies isolated from day to day, in contrast to the consistently high incidence in daily specimens from persons with celiac disease.

Since it was not possible to explain these results on the basis of diet, an investigation was carried out on new-born infants to study the factors responsible for the appearance of Lactobacillus bifidus. These experiments seemed to warrant the following conclusions: 1. The difference in the chemical composition of the food of the breast fed and artificially fed infant does not adequately explain the marked difference in the flora. 2. There are sources of Lactobacillus bifidus other than breast milk. 3. A detailed study of the organism showed that on dissociation forms are obtained which one could not accept as Lactobacillus bifidus when the ordinary criteria of diagnosis are used. This probably explains our failure to isolate a characteristic form of Lactobacillus bifidus from sixty samples of breast milk.

REDUCTION OF METHYLTHIONINE CHLORIDE, U. S. P. (METHYLENE BLUE) BY THE BLOOD OF YOUNG INFANTS. DR. CARL H. SMITH, New York.

This article will be published in full in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

MINERAL BALANCE IN NORMAL INFANTS. DR. M. A. WHEATLEY and DR. S. Z. LEVINE, New York.

A method is presented for the accurate study of mineral balance in infants, including analyses of diet and of the urine, stools and cutaneous excretions. Two normal infants were studied for two five day periods at 72 and 84 F., the temperatures being maintained at a constant level throughout each period.

The results indicate that the cutaneous excretion of minerals is quantitatively dependent on the environmental temperature and suggest that further study be made of the effect of other extraneous variables.

The magnitude of the elimination of potassium, sodium, and chlorine through the skin, particularly at the higher temperature, shows that this channel of elimination must be included in accurate studies of mineral balance and in studies of shifts of intracellular and extracellular water within the body.

DISCUSSION

DR. A. T. SHOHL, Boston: It seems to me that the data available would enable one to calculate the amount of minerals excreted in sweat and in the perspiration water exchange as well as in the mineral exchange in the skin.

I should like to ask a question regarding the relation of the removal of sweat to the nature of the excretion. Is it not possible, as some have suggested, that the material which dries on the skin alters the composition of the sweat which is secreted? And is it worth while to see whether, if one bathes babies every day or half a dozen times a day, the secretion is altered under those conditions?

DR. W. W. SWANSON, Chicago: Miss Iob and I have determined the minerals excreted in the sweat in infants. We have not, however, determined the excretion of minerals in the sweat, stools and urine on any one infant, as this requires a great amount of work and care. We found, as Dr. Wheatley has so ably shown, that a considerable amount of the minerals absorbed found their way through the skin. Dr. Gamble, after studying our paper on sweat, pointed out that tempera-

ture probably would influence the loss of minerals in the sweat. I am pleased to know that this suggestion has been confirmed by Dr. Wheatley's study.

DR. S. Z. LEVINE, New York: Nobody, except possibly Dr. Swanson, realizes the difficulties encountered in this work, and Dr. Wheatley is to be congratulated. She undertook this study for two reasons: (1) to study the rôle of elimination and (2) as part of a nutritional study of infancy dealing with the organic metabolism as determined by studies of balance of energy, protein, fat, carbohydrate and water over long periods.

These studies of mineral balance complete the knowledge of the fate of all the essential elements requisite in an adequate dietary for infants, with the exception of the vitamins, which are not amenable to studies of balance with the technical methods available.

Vasti, at Johns Hopkins University, found that under environmental conditions at which visible perspiration is eliminated and in the complete absence of activity of the sweat glands, the insensible perspiration contains no inorganic elements (chlorides). We confirmed this in observations on two infants and one adult. The results obtained by Dr. Wheatley indicate that even at 72 F. the sweat glands are active, as evidenced by the frequent appearance of beads of perspiration on the face of the infant at the time of feedings and shortly after. This undoubtedly explains why the method proposed some time ago by Newburgh for predicting the metabolism from the insensible perspiration in adults does not work in infants under conditions of maintenance, although it holds in the basal state.

As Dr. Shohl pointed out, it would be interesting to calculate the composition of sweat, and we are in the process of so doing. It is also interesting that even on a lower proportionate intake the younger infant studied retained in his body more potassium than the older infant, suggesting an accelerated growth impulse in the younger infant.

CARBOHYDRATE METABOLISM: III. EFFECT ON THE OXIDATION OF DEXTROSE OF VARIATIONS IN THE INTAKE OF SALT AND WATER. DR. JOSEPH A. JOHNSTON and DR. JOHN MARONEY, Detroit.

This article will appear in full in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

FAT METABOLISM OF PREMATURE INFANTS. DR. L. EMMETT HOLT JR., DR. HERBERT C. TIDWELL, DR. H. L. FARROW and DR. SARAH NEALE, Baltimore.

In studies of balance which we previously made on normal infants (*Acta paediat.* **16**:165, 1933) it was found that (1) short-chain saturated fatty acids are better absorbed than longer-chain ones; (2) unsaturated fatty acids are better absorbed than saturated ones; (3) the percentage of acids containing an unsaturated linkage is of greater significance than the iodine value (total unsaturation); (4) the low melting point of most readily absorbable fats appears to be a mere coincidence and not the determining factor in the absorption of fat.

In studying a series of animal and vegetable fats, we found that (1) breast milk fat and human body fat are more completely absorbed than butter; (2) even better absorption occurs in the case of certain vegetable fats (olive oil, soya bean oil) which contain a high percentage of unsaturated fatty acids; (3) the proprietary mixtures of fat designed for infant feeding are no better absorbed than butter fat and in some instances (e. g., S. M. A. milk fat) are not quite as well absorbed. The differences in the absorption of these various fats by normal infants are comparatively small and of little practical significance. In the case of poor absorbers of fat, such as premature infants, however, these small differences tend to become large and assume practical importance. Premature infants usually absorb only about half of the butter fat which they receive; whereas if olive oil or soya bean oil is substituted for the butter fat, absorption is increased to 75 per

cent or 80 per cent of the intake. The improvement in absorption of fat is reflected in the weight curve.

In an attempt to improve absorption still further, we employed some pure preparations of olein and linolein. Significant differences in the behavior of these two preparations were not noted. Neither gave figures for absorption as high as had been obtained with olive oil or soya bean oil. The interpretation of the last finding is not clear. It is possible that the three infants used in these experiments were especially poor absorbers of fat, and it is also possible that a single pure ester, such as was used in these experiments, does not represent an ideal food. The latter view is in harmony with the animal experiments recently reported by Cox (*J. Biol. Chem.* **103**:777, 1933).

DISCUSSION

DR. BENGT HAMILTON, Chicago: I could not help being interested in hearing how Dr. Holt had juggled the lines around to fit his data, with such fortunate results. I conclude from this that conditions have changed a great deal at Johns Hopkins University since I was there—that correlation coefficients are no longer being calculated.

DR. S. Z. LEVINE, New York: Of course, Dr. Holt will readily admit that the evidence which he presented is only half the story. One would like to know what happens to the fat after it is absorbed from the alimentary tract. It is not known whether that fat is actually utilized within the body or whether at the end of a long period it is excreted in the stools or otherwise lost from the body after the period of observation has terminated. I should like to know the duration of the longest period of observation which was carried out on the premature infants.

DR. L. EMMETT HOLT, Baltimore: Dr. Hamilton's criticism that we failed to calculate correlation coefficients is in order. I shall, however, be much surprised if the calculated slope of the lines relating the percentage of absorption to the intake of fat proves to be very different from those which we have shown.

It is true that figures relating to retention do not indicate what happens after absorption. The question raised by Dr. Levine as to whether babies might not absorb from the intestine a fat which they could not utilize and which they would subsequently excrete in the bowel, is, I confess, one that we cannot answer at this time. We noted high retention during the third week of feeding with the vegetable fats mentioned, but we have no chemical data on infants who have been so fed for a longer time. The rapid gain in weight is, however, not a transient phenomenon; we observed that at least as late as the fifth week of special feeding.

TREATMENT OF EXPERIMENTAL NUTRITIONAL EDEMA WITH CONCENTRATED SOLUTIONS OF SERUM ALBUMIN. DR. A. A. WEECH and DR. E. GOETTSCH, New York.

Experiments are reported in which six dogs suffering from nutritional edema and exhibiting hypoproteinemia were given transfusions of concentrated solutions of homologous serum albumin. In three instances complete elimination of edema resulted, and in the other three instances the degree of edema was definitely lessened, although complete disappearance did not occur. The degree of therapeutic success was apparently determined by the resulting level of albumin in the serum and by the relation of this level to the concentration of albumin which had previously been associated with the development of edema.

The transfusions resulted in an increased concentration of albumin and a decreased concentration of globulin in the serum. The fall in the level of globulin was shown to depend on an increase in the volume of the total plasma. This increase was significantly greater than the volume of the solution injected and indicated an immediate drawing into the circulation of an appreciable quantity of previously extravascular fluid. The increase in the volume of plasma caused an

immediate fall in the percentage of circulating red cells, so that, as measured by the usual criteria, the animals became more anemic. A slight but scarcely significant rise in the proteins of the plasma resulted when the anemia was relieved by transfusing a suspension of washed erythrocytes in physiologic solution of sodium chloride.

DISCUSSION

DR. STUART MUDD, Philadelphia: Is the fall in the hematocrit reading in such instances due to a decreased number of red cells? Might it be due to decreased volume of the cells?

DR. A. A. WEECH, New York: I can hardly conceive of a change in the formula of red cells sufficient to produce anemia comparable to that caused by a decrease in red cells. We had thought earlier that some red cells were being taken out in the spleen, and in an earlier set of experiments we removed the spleen, without finding any difference in the nature of the results. In this group I believe that the ability to provide the change in blood protein and the change indicated by the hematocrit suggest that to a large extent these changes were due to a decreased volume of the cells.

EFFECT OF SUPRARENALECTOMY ON THE SALT METABOLISM OF RATS. DR. MITCHELL I. RUBIN and DR. ELIZABETH T. KRICK, Philadelphia.

Studies of the salt balance following bilateral suprarenalectomy in white rats are reported. These showed that during suprarenal insufficiency there occurred a marked loss of sodium, potassium, calcium, magnesium, phosphorus, chlorine and nitrogen from the body, resulting in most instances in a negative balance. It was found that during the diuresis which occurs immediately after suprarenalectomy there was a great loss of sodium in the urine. This negative sodium balance gradually decreased in severity as the animal became progressively more dehydrated. Other salts were also lost during this early postoperative period.

Eighty per cent of the suprarenalectomized rats showed symptoms of suprarenal insufficiency. These rats could be relieved of their symptoms and death could be prevented by replacing their drinking water with a solution of 0.9 per cent sodium chloride or a combined salt solution. Studies of the salt balance on one pair of rats showed that when they were given modified Ringer's solution or a 0.9 per cent solution of sodium chloride, the salt balances, including that of nitrogen, returned to a positive retention. In each instance, when the 0.9 per cent solution of sodium chloride or salt solution was replaced with distilled water for drinking, the balance became insufficient. It could be restored again, however, if either of these solutions was given.

It was demonstrated that while these salt-treated suprarenalectomized animals seemed healthy in every way, their weight curves fell below those of normal litter mates. These experiments suggest that while the suprarenal gland apparently plays an important part in the regulation of the salt and water metabolism, there must be other factors of great importance.

DISCUSSION

DR. L. EMMETT HOLT, Baltimore: All the members regret that they cannot be in two places at once; it is rather an unfortunate coincidence that two papers on the suprarenal gland—this one and one by Dr. Harrop in the next room are being read at the same time.

Dr. Rubin has shown conclusively that in the rat the feeding of salt increases weight; Dr. Harrop's work indicated that it fails to do so in dogs, since the animals refuse to eat and can be restored to health only by the intravenous administration of lecithin. I wonder whether Dr. Rubin has any explanation to offer as to the difference between the dog and the rat.

DR. S. Z. LEVINE, New York: There was one point which I did not understand. It seemed from the tables shown by Dr. Rubin that the negative balance following suprarenalectomy was always the result of reduced intake rather than increased excretion. I wonder whether he had control rats in which he reduced the intake to the same level as in the rats operated on to see whether he could reduplicate the findings in the control group. In other words, I believe that an additional group of control animals on a reduced intake might have strengthened the evidence.

DR. MITCHELL I. RUBIN, Philadelphia: We are unable to answer Dr. Holt's question. Swingle and his associates in a recent publication reported that they were able to maintain suprarenalectomized dogs on sodium chloride for a certain length of time. These animals, however, finally succumbed. It is possible that there is a difference peculiar to the species which accounts for the difference in the results obtained.

In regard to Dr. Levine's question, though the rats consume a decreased amount of food during insufficiency, yet the output of salt per gram of food during the period of insufficiency is greater than the output of salt per gram of food during the control period. Studies are in progress to determine the output of salt per gram of food in rats maintained on a decreased ration.

CALCIUM AND PHOSPHORUS METABOLISM IN INFANTILE TETANY. DR. T. B. PINCUS and DR. I. F. GITTLEMAN, Brooklyn.

Experiments on calcium and phosphorus balance were done on two children, one of whom was suffering from rickets complicated by tetany; the other had tetany due to a low calcium level, without evidence of rickets. The first was treated with vitamin D milk, while the latter was given parathyroid extract. The effect of both forms of treatment on the calcium and on the phosphorus metabolism was also studied. The calcium and phosphorus partitions in the urine and stools are given. The calcium and phosphorus concentrations in the serum were determined at the various periods of the experiments. The results obtained in the case of tetany caused by a low calcium level compare with the findings that obtain in cases of parathyroprivia, i. e., a low serum calcium concentration, a high serum phosphorus concentration and a low urinary calcium excretion. Under treatment with parathyroid extract the serum calcium concentration became normal, and the phosphorus serum concentration decreased. There was a striking excretion of phosphorus in the urine. The excretion of phosphorus in the stools diminished. The excretion of calcium in the urine increased, while that in the stools decreased.

The results obtained in the balance experiment in the case of rickets complicated by tetany differ from those in the case just described in that the serum phosphorus was normal: There was no striking partition of phosphorus in the urine, i. e., no negative phosphorus balance was obtained. The calcium metabolism was comparatively little affected by treatment with parathyroid extract.

Withdrawal of the parathyroid extract brought the child back to the convulsive state, with the chemical changes noted on admission. There was gradual improvement so that two weeks after the last balance experiment was performed and with no further treatments with parathyroid extract we found normal phosphorus and calcium concentrations in the blood, and the child has since remained free from symptoms.

DISCUSSION

DR. A. T. SHOHL, Boston: Perhaps Dr. Albright could be persuaded to make some remarks.

DR. FULLER ALBRIGHT, Boston: I agree with Dr. Pincus that this was a case of parathyroid hypofunction.

Recently, I had an opportunity to see a similar case at the Baker Hospital; a child just delivered had convulsions. This child had the same low serum calcium

level and the same high serum inorganic phosphorus level as the patient described by Dr. Pincus. At the end of about two weeks the condition cleared up; it was transient and typical of hypoparathyroidism. There is no question about the diagnosis; this condition is 100 per cent different from rachitic tetany. Did the mother show any signs of tetany?

DR. J. B. PINCUS, Brooklyn: The mother was perfectly normal.

DR. FULLER ALBRIGHT, Boston: The mother was perfectly normal in our case also.

DR. RUSTIN MCINTOSH, New York: I do not entirely agree with Dr. Albright that this case unquestionably represents hypoparathyroidism. In premature infants whose calcium and phosphorus levels in the blood are studied at an early age, a phosphorus content of 7 mg. per hundred cubic centimeters is not uncommon. This may be part of the normal physiology of early life and should perhaps be studied further from that point of view.

SPECTROGRAPHIC DETERMINATION OF LEAD IN BLOOD. DR. HAROLD BLUMBERG and DR. T. F. MCNAIR SCOTT, Baltimore.

In a previous report it was demonstrated that by means of the spectrograph lead may be detected easily in the blood in clinical cases of lead poisoning, while it shows only as a faint trace in normal blood. This test, which requires the ash from 3 to 5 cc. of blood and which may be completed within from twelve to twenty-four hours, appeared to be an aid to the clinical diagnosis of plumbism. Work on the method has been extended in a study of about twenty-five cases of clinical lead poisoning, a similar number of mild cases of exposure, and a larger series of normal controls. The results of these studies on blood, as well as the spectrographic detection of lead in cerebrospinal fluid and tissues, have proved interesting and useful. Of particular interest is the fact that the lead content of the blood may remain high for many months after a heavy "leading," despite the absence of symptoms.

The method was made quantitative by the preparation of standard spectrograms of a lead-free artificial blood ash consisting of sodium chloride, calcium phosphate, potassium phosphate and ferric oxide, to which lead nitrate was added in varying concentrations. By a comparison of the number and intensity of the spectrographic lines for lead of a given blood ash and the lines on the standard plates, the lead content of the blood may be estimated. In terms of absolute sensitivity, it was found that 0.0001 mg. of lead could be detected. Relative to whole blood, the limit of detection was 0.005 mg. per hundred cubic centimeters of blood.

From the data secured the following values appear to obtain for blood lead in milligrams per hundred cubic centimeters of blood:

"Normal" lead (negative result)	0.005-0.05
Exposure to lead (doubtful result)	0.05-0.1
Lead poisoning or convalescence from lead poisoning (positive result)	0.1-0.5

The conclusions drawn in regard to the value of the spectrographic determination of blood lead are: 1. A negative result eliminates lead poisoning as a diagnostic consideration. 2. A doubtful result indicates mildly abnormal exposure, but rules out clinical lead poisoning. 3. A positive result indicates lead poisoning with more or less marked clinical symptoms or a state of convalescence from lead poisoning.

DISCUSSION

DR. MAX TRUMPER, Philadelphia: Have any studies been made of the quantitative lead and the stippling count? If so, what is the relationship?

DR. HAROLD BLUMBERG, Baltimore: We did not carry out close studies correlated with the concentration of lead, but I believe that the relation between

stippling and the concentration of lead may constitute an anomaly, because we have found that stippling may disappear and the concentration of lead remain fairly heavy. We have not carried out definite studies.

THE METABOLISM OF CARBOHYDRATES IN A CASE OF GALACTOSURIA. DR. HOWARD H. MASON and DR. MARY E. TURNER, New York.

A metabolic study of a case of galactosuria in early infancy has been made. This case was characterized by lack of growth, anemia, albuminuria and a large liver and spleen.

A normal tolerance for dextrose and fructose and a decreased tolerance for galactose and lactose were found. When galactose or lactose was administered, a considerable portion was excreted in the urine as galactose. The blood dextrose (finger-tip method) did not vary from the normal range when the patient was on a milk-free diet. The addition of milk to the diet caused a depression of the level of the blood dextrose, which did not rise until after the level of the blood galactose dropped. Administration of epinephrine after a milk-free meal caused normal elevation of the blood dextrose content; after a meal containing lactose the blood dextrose level was elevated, and the galactose level was not affected by epinephrine. When insulin was given after a lactose-free meal, the blood dextrose level was depressed, and slight shock occurred. After a meal containing lactose, insulin caused an immediate rise in the total blood sugar level. The blood galactose level was considerably elevated, while the blood dextrose level was lowered, but no evidence of shock was present.

It is suggested that the low blood dextrose level and the large liver were due to excessive storage of glycogen in the liver, and that the clinical symptoms were due to the abnormal distribution of the blood sugars. The metabolism of carbohydrates after the administration of epinephrine was normal, while after the administration of insulin some factor caused mobilization of galactose in large quantities.

DISCUSSION

DR. E. A. PARK, Baltimore: We have had two infants with this condition at the Harriet Lane Home and were nonplused as to what was the matter with the first one until Dr. McIntosh told me of the case on his service which Dr. Mason had diagnosed and which he has just reported. Then I realized that our infant was suffering from the same condition. Our cases were in a brother and sister; unfortunately, both died, before we had the opportunity to do more than identify the galactosuria. I can add to the knowledge of the subject by stating that in both our cases cirrhosis of the liver was present. I think that these cases are the only two of this kind which have been studied post mortem. They will be reported by Dr. Hugh Josephs.

DR. BENJAMIN KRAMER, Brooklyn: Cases associated with specific disturbances in carbohydrate metabolism are not uncommon. In the condition described by von Gierke there is enlargement of the liver and kidneys, with accumulation of glycogen in enormous quantity in these organs. The administration of epinephrine is without effect on the blood sugar. Recently, I saw a case in which hepatomegaly was an outstanding clinical finding and was associated with marked hypoglycemia. The administration of epinephrine was without effect, and levulose and galactose produced no change in the blood sugar level. At no time was it possible to demonstrate the presence of sugar or ketone bodies in the urine. The child died, and extensive fatty degeneration of the liver was found post mortem. Attempts to demonstrate glycogen in the liver were unsuccessful.

In going over the literature I found three cases of the kind reported in one family. Unfortunately, only one blood sugar determination was done; the value obtained was 80 mg.

I might add that complete quantitative studies of the blood serum revealed no changes other than the marked diminution in the concentration of the blood sugar. This case is one of fatty infiltration of the liver in which glycogenesis is interfered with, giving rise to marked hypoglycemia.

DR. L. EMMETT HOLT, Baltimore: I do not see the relation between Dr. Kramer's case of fatty liver and Dr. Mason's case of galactosuria.

It is worthy of comment that in one of the cases that came to autopsy in Baltimore, Dr. Arnold Rich was able to demonstrate an anomaly of the liver which he believed to be related to the anomaly of metabolism, namely, an acinar arrangement of the liver cells. Last summer, at the International Pediatric Congress in London, Ylppö reported a similar histologic anomaly in several infants with congenital cirrhosis of the liver. Studies of the sugar metabolism, however, were not described.

VAPOR PRESSURE OF BLOOD BY HILL'S THERMO-ELECTRIC METHOD. DR. ROBERT W. CULBERT, New York.

In 1930, Margaria determined the normal vapor pressure of adult defibrinated blood, using the thermo-electric method suggested by A. V. Hill. The present report deals with the application of this method to the determination of normal values of vapor pressure for infants' and children's blood.

The method depends on the difference in temperature attained by opposite faces of a symmetrically wound thermopile in an atmosphere of 5 per cent carbon dioxide; on one face is a piece of filter paper saturated with defibrinated blood, while on the other is placed a similar piece of filter paper soaked in a standard solution of sodium chloride. The difference in temperature resulting from the unequal rates of evaporation from the two faces produces an electromotive force proportional to this difference, which is read on a sensitive galvanometer. The thermopile having been calibrated previously with solution of sodium chloride of accurately known concentration, the vapor pressure of the blood can be calculated in terms of the standard solution. The mean value for thirty boys was 0.9006 ± 0.0020 potential difference, and for twenty girls 0.9053 ± 0.0026 potential difference, expressed as grams of sodium chloride per hundred grams of water. There is no statistical difference between the values for boys and those for girls. Margaria, whose values for adults were somewhat higher, showed that statistically the vapor pressure of the blood of men was greater than that obtained for women.

NUTRITIONAL VALUE OF SLIGHTLY RANCID FAT. DR. DOROTHY V. WHIPPLE, Philadelphia.

The chemical condition of the fat of a ration has been found to be an important factor in determining the nutritional value of the ration.

Three comparable groups of rats were fed a fat-free basal diet adequate in all known dietary essentials. One group was given in addition to the basal ration 0.1 cc. daily of fresh neutral fat; the second group received 0.1 cc. daily of slightly rancid fat (peroxide value from 15 to 20 millimols per kilogram), and the third group was given no fat. The animals receiving the good fat grew normally and remained in apparent good health for the duration of the experiment (two hundred and eighty-eight days). The animals in the fat-free group grew at a slower rate for the first five and a half months, then began to lose weight and finally died with symptoms of the fat deficiency disease described by Burr and Burr. The rats receiving the oxidized fat grew at about the same rate as the fat-free controls and showed symptoms similar to those with the fat deficiency disease within the same period of time; their length of life, however, was longer than that of the fat-free animals.

A curative experiment was done in which comparable trios of animals suffering from severe fat deficiency disease were fed: (1) neutral fat, (2) partly oxidized

fat or (3) no fat. The animals receiving neutral fat were cured of the disease; those receiving no fat died, while those receiving oxidized fat died more quickly than the fat-free controls.

It is tentatively concluded that partly oxidized fat is unable to replace neutral fat in the diet, possibly owing to the destruction of the double bonds in the nutritionally essential fatty acids, and that there may be a toxic factor produced in the fat by the oxidative process.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

May 10, 1934

MARTHA WOLLSTEIN, M.D., *Chairman*

HARRY BAKWIN, M.D., *Secretary*

AMYLOIDOSIS IN AN EIGHT YEAR OLD CHILD. DR. J. BREM.

The patient is an 8 year old colored girl. The conditions at birth and the family and past histories are irrelevant. There has been no exposure to tuberculosis. Two and one-half years ago she began to have fever, night sweats, loss of weight and an unproductive cough. She was taken to the Metropolitan Hospital, from which she was transferred to Sea View Hospital, with a diagnosis of pulmonary tuberculosis and tuberculous peritonitis.

At Sea View Hospital she was found to be markedly underdeveloped and undernourished. Nine months after admission enlargement of the liver was first noted, and from then on the liver increased steadily in size. Albuminuria was also present.

Because of the marked enlargement of the liver and her stunted growth, the child was transferred to Mount Sinai Hospital for further study. On admission she appeared physically and mentally retarded. General physical examination gave negative results, except for the markedly enlarged liver. A blood count revealed secondary anemia. The blood chemistry was normal. Albuminuria persisted. Liver function tests gave normal results. The Wassermann reaction of the blood was negative on two occasions. The congo red test for amyloidosis showed 100 per cent retention of the dye at one hour. This test was repeated twice at an interval of about two months, and each time 100 per cent retention was noted. Although the child had irregular bouts of low grade fever from 101 to 102 F., at no time was there evidence of any suppuration or other infection than the acid-fast process. Roentgenograms of the bones were normal, except for thickening and increase in the density of the epiphyseal ends of the long bones, indicating some disturbance in growth. The child was given 100 Gm. of whole liver daily and a diet high in vitamins for a period of two months. Subsequently, liver meal, 5 Gm. three times daily, was substituted for the whole liver. Four months after this diet was instituted the liver appeared somewhat smaller, but the congo red test still showed 100 per cent retention. At this time a round, freely movable mass was noted below the right border of the liver. Intravenous pyelography revealed this to be a somewhat enlarged, irregular right kidney.

The interesting feature of this case is the extreme amount of amyloidosis without any suppurative focus. Usually, amyloidosis occurs in the presence of suppuration, but here no focus except the tuberculous process was demonstrable. Another interesting point is the extreme retardation in growth and development, and the third point is the relative well-being of the child in the presence of the amyloidosis.

SEQUESTRATION OF THE RIGHT UPPER LOBE IN THE COURSE OF EMPYEMA; RECOVERY WITH PERSISTENT PNEUMOTHORAX. DR. F. W. SOLLEY.

Veronica M. was first admitted to the Babies Hospital on June 11, 1932, with pneumonia and empyema in the right side of the chest, which had been detected by thoracentesis by the family physician. Closed drainage was instituted, followed by simple open intercostal drainage and, later, resection of ribs. The organism was a pneumococcus type I. Because of persistent elevation of temperature and other signs of inadequate drainage, another thoracotomy was performed a month after the first one; a large piece of necrotic lung tissue, which was probably from the right upper lobe, was found lying free in the pleural cavity and was easily removed. Gradual recovery from the pleural infection followed. At discharge, on October 26, a pneumothorax cavity persisted, although the wound in the chest was closed.

The patient was readmitted to the hospital in March 1934 because of an infection of the upper respiratory tract. The chief findings on admission were fever and tonsillitis. Although the tonsillitis improved, the fever persisted, and a roentgenogram finally revealed a collection of fluid in the area of pneumothorax in the right side of the chest. Thoracotomy was performed on April 9, and a large amount of pus was evacuated from the right pleural cavity. The temperature promptly dropped to normal, and the child is now convalescent from this operation.

This is an exceedingly rare condition. There are few cases reported in the literature, and the only ones which I have been able to find so far have followed the aspiration of a foreign body. A case was reported in 1904 following the aspiration of a grain stalk (Budinger: *München. med. Wchnschr.* **51**:1874, 1904). This case, to my mind, represents a marked degree of a condition more frequently encountered and usually called "aputred anaemic necrosis" (Morris Gleich: *Arch. Pediat.* **49**:258 [April] 1932). A small area of necrosis of this type clears up without sequestration. In this case I believe that we were dealing with a tremendous necrosis, probably of the same type, followed by so much interference with circulation that the entire upper lobe eventually underwent sequestration.

Dr. Howard Lillienthal kindly discussed this case when I presented it last October before the Surgical Section and said that he had never seen a similar one. He thought that the child would have to be kept under close observation to see whether recurrent empyema would develop, which is what happened six weeks ago. He also thought that deformity of the chest might possibly develop in sufficiently marked degree to justify radical surgical intervention. In either event, extensive thoracoplasty might be necessary, with removal of a sufficient number of ribs to collapse the lung and thus obliterate the pneumothorax cavity. As long as the child continued well without thoracic deformity, Dr. Lillienthal strongly advised against this radical procedure.

DISCUSSION

DR. MARTHA WOLLSTEIN: No case of this kind has been seen at the Babies Hospital, and when Dr. Solley brought the specimen we were surprised to find that it really was a piece of lung, apparently an entire lobe.

RAT-BITE FEVER. DR. W. S. ANDERSON.

A 7 month old colored boy was admitted to the children's clinic of the New York Hospital on Feb. 15, 1934, because of swelling of the middle finger of the left hand, of one month's duration. There was no family history of syphilis or tuberculosis. The mother's Wassermann reaction was negative on two occasions. Except for occasional colds, the patient had been well up to the present illness.

One month before admission the mother saw a rat bite the middle finger of the patient's left hand. Profuse bleeding followed, which lasted about an hour. One week later the mother noticed that the finger was swollen. The patient was taken to a physician, who incised the finger and obtained pus. In spite of this the finger continued to swell, and the patient became very irritable. Nine days

before admission, three weeks following the bite, a temperature of 40 C. (104 F.) developed, which lasted twenty-four hours. The patient slept poorly, and the irritability continued, but the temperature remained normal up to the day of admission, when it rose to 38.4 C. (101.1 F.).

Physical examination showed a fairly well developed and well nourished infant of 7 months, weighing 7,440 Gm., who did not appear acutely ill. The temperature was 38.4 C. (101.1 F.). No eruption was noted on the skin. There were shotty lymph nodes in the left axilla and pea-sized nodes in the left epitrochlear region. The nasal mucosa was injected, and there was a profuse mucopurulent discharge. Moderate injection of the posterior part of the pharynx was present. The lungs and heart were normal. On examination of the abdomen the tip of the liver was felt below the costal margin. The spleen was not felt. The middle finger of the left hand showed marked swelling of the proximal and middle phalanges to from three to four times the normal size. There were moderate induration, tenderness and redness, but no local heat. The incision on the dorsal aspect of the middle phalanx was well healed.

The laboratory reported: hemoglobin, 100 per cent; red blood cells, 4,320,000; white blood cells, 17,500; 71 per cent adult polymorphonuclears; 1 per cent immature polymorphonuclears; 26 per cent lymphocytes, and 2 per cent monocytes. The urine was normal. The Wassermann reaction was negative. An intradermal injection of 0.1 mg. of tuberculin gave a negative result. Two blood cultures were sterile. A roentgenogram of the left hand revealed marked swelling of the soft tissue about the proximal and middle phalanges. There was evidence of a slight destruction of bone in the middle phalanx.

On the second day after admission the temperature dropped to normal, where it remained for four days. It then rose to 39.6 C. (103.3 F.), and the patient became irritable. There was some increase in the pharyngitis, and moderate injection of both ear drums was noted. The finger remained unchanged. Within three days the temperature had subsided.

The temperature remained normal for four days and again rose to 40 C. (104 F.), at which level it remained for four days. Examination revealed definite generalized glandular enlargement. The left epitrochlear and axillary glands were larger than the right. At this time there appeared on both cheeks and over the chest several brownish red, urticarial-like lesions from 1 to 2 cm. in size. Some of these lesions were transient and disappeared within twenty-four hours. There was no change in the size of the finger. Blood was withdrawn from the patient, and 1 cc. was injected subcutaneously into each of three mice. A black, crusted ulcer developed at the site of injection, and at the end of a week Spirochaeta morsus-muris of rat-bite fever was found by dark field examination.

After five days of normal temperature the fourth febrile rise occurred, with elevation of the temperature to 39.4 C. (102.9 F.), which lasted for four days. The irritability returned, and new urticarial lesions appeared on the face and lower part of the abdomen. The generalized glandular enlargement increased, and the tip of the spleen became palpable. Another mouse was given an intraperitoneal injection of the patient's blood. No lesion developed at the site of the injection, but at the end of a week Spirochaeta morsus-muris was again found by dark field examination. Several attempts to find the spirochete by direct examination of the patient's blood were unsuccessful.

During the next afebrile period of six days the patient improved rapidly. The swelling of the finger subsided, and the irritability disappeared. The fifth bout of fever was mild, lasting only two days, with a temperature of 38.2 C. (100.7 F.). Only one or two cutaneous lesions were noted. After six days without fever the sixth febrile rise occurred, lasting two days, with a temperature of 38.2 C. (100.7 F.).

Despite the tendency to spontaneous improvement, it was deemed advisable to give the patient three intravenous injections of neoarsphenamine at weekly intervals, using 10, 15 and 20 mg., respectively, per kilogram of body weight. After the first injection the temperature rose to 39.2 C. (102.5 F.) and remained between

38 and 39 C. (100.4 and 102.2 F.) for four days. This may have been a reaction to the neoarsphenamine. The second and third injections caused no rise in the temperature, and the patient remained entirely afebrile up to the time of discharge two weeks later. At the time of discharge, on March 16, the finger was practically normal in size, but the generalized glandular enlargement remained. The patient has been seen in the outpatient department several times since discharge and has remained entirely well.

DISCUSSION

DR. W. S. ANDERSON: We considered this a typical case. Such cases occur relatively infrequently. Bayne-Jones reviewed the literature in this country and collected data on eighty-one cases up until 1931. Of these, he considered seventy-six to be typical cases. Since 1931, seven cases have been reported, two from New York state. This patient came from Connor Street on the lower East Side.

DR. JOHN CAFFEY: Was there any lymphadenitis of the extremity involved?

DR. W. S. ANDERSON: There was definite lymphadenitis involving the epitrochlear and axillary glands of the involved extremity. This was present when the patient was admitted to the hospital. It is interesting that the lymphadenopathy became generalized at the third febrile rise at the same time that the rash was noted.

GENERAL MILIARY TUBERCULOSIS IN AN INFANT AGED THREE MONTHS. DR. W. MORGAN HARTSHORN.

J. P., aged 2 months, was admitted to Polyclinic Hospital on Dec. 25, 1933. The chief symptoms were fever and cough.

The father and mother were alive and well, and no family history of tuberculosis was obtainable. The patient was the first child and had been born in Polyclinic Hospital by forceps delivery. The weight at birth had been 7 pounds (3,175.14 Gm.). The patient nursed for three weeks and was then given a formula of modified milk. After leaving the hospital the baby gained satisfactorily. The mother noticed that the child had frequent attacks of coughing. Three days before admission coryza developed, and the attacks of coughing became more pronounced. As the child appeared to have fever, he was brought to the emergency department.

Physical examination showed a well developed infant weighing 9¼ pounds (4,195.7 Gm.). There was a slight nasal discharge. The throat was somewhat congested. The patient was slightly anemic. The heart was normal. There was slight beading of the ribs. The ears were normal. Many crackling râles could be heard over the front and back of the chest. The abdomen was normal. The temperature was 101.5 F., the pulse rate 130 and the respiratory rate 30.

A blood count showed 3,850,000 red cells and 31,400 white cells, with 48 per cent polymorphonuclears, 40 per cent lymphocytes, 1 per cent eosinophils, 2 per cent basophils and 6 per cent myelocytes. Urinalysis gave normal results.

The temperature ranged from 100 to 103 F. during the patient's stay in the hospital. A roentgenogram showed diffuse involvement of the right lung. There was marked displacement of the heart to the right, possibly due to occlusion of the right bronchus. Later roentgenograms showed the same condition in the right lung, with emphysema and tubercles in the left lung. Enlargement of the mediastinal glands was present.

On Jan. 22, 1934, a brassy cough developed. There was dulness on the right side, with high-pitched, stertorous breathing. The liver and spleen were palpable. There was continual loss of weight. Signs of obstruction were present in the right bronchus, but bronchoscopy was not advised. The Mantoux test gave positive results. On February 22 the condition in the chest was about the same; the child was weaker, and the temperature ranged from 101 to 102.6 F. On March 19 stiffness of the neck and opisthotonos developed. Lumbar puncture showed 22 cells per cubic centimeter, 16 of which were lymphocytes. A pedicle was present. No tuberculosis was found. On March 23 the patient suddenly became dyspneic and died.

The report of the autopsy was as follows: Both lungs were enlarged with many nodules on the surface. On the base of the right lung was a small localized abscess. There were ulceration of the trachea and general enlargement of all the lymphatic glands. The spleen and liver showed many conglomerate tubercles. The intestines showed ulceration. The kidneys showed occasional tubercles.

The diagnosis was typical generalized abdominal and peritracheal tuberculosis, with erosion of the trachea, tuberculous pneumonia and typical miliary tuberculosis, with involvement of the liver, spleen, kidneys, lungs and choroid plexus (typical because histologic examination showed tubercles with few giant cells, and the condition did not represent a complete picture of tuberculosis).

DISCUSSION

DR. MARTHA WOLLSTEIN: Were you able to trace the source of the infection?

DR. W. MORGAN HARTSHORN: We were not able to determine the source.

SCHISTOSOMIASIS. DR. HUGH F. LEAHY.

J. R., a Puerto Rican girl, aged 12 years, was admitted to St. Vincent's Hospital on July 14, 1933, with the chief complaint of diarrhea. Birth and feeding had been normal. She had spent the first six years of her life in Puerto Rico and the remaining six in New York City. While living in Puerto Rico the patient experienced a severe attack of diarrhea at the age of 1½ years. Her two brothers and two sisters suffered from a similar condition. It was characterized by prominence of the abdomen and marked diarrhea, which persisted for three months. The patient is the sole survivor of the five afflicted. There was no other illness of importance.

The present illness began one week before admission, with severe diarrhea associated with generalized gripping abdominal pain. The stools were said to be liquid and whitish like mucus; no blood was noted. It is said that worms were passed in almost every stool until the day before admission; these varied between 1 and 15 cm. in length and were actively motile. The patient vomited twice, and there had been moderate anorexia, although previously the appetite had been voracious.

Physical examination revealed a well developed but thin girl aged 12 years, who did not appear acutely ill. The temperature was normal. The chief findings were in the abdomen, which was moderately distended. The liver was palpable five fingerbreadths below the costal margin; the edge was smooth and sharply defined. There was no tenderness, and no nodules were felt. The splenic edge was palpable four fingerbreadths below the costal margin and extended almost to the midline. It was firm, smooth and nontender. The only other important physical finding was generalized lymphadenopathy, which involved the cervical, axillary, inguinal and epitrochlear lymph nodes. The lymphatic glands were slightly larger than peas; they were firm and not tender.

On admission the blood showed hemoglobin, 84 per cent; red cells 4,380,000, and white cells 4,100, with 47 per cent polymorphonuclears, 42 per cent lymphocytes, 2 per cent monocytes and 9 per cent eosinophils. There were no stippled cells or malarial parasites. The urine was normal, as were the throat and vaginal smears. On admission the patient presented many interesting problems in differential diagnosis. The enlarged liver and spleen, generalized lymphadenopathy and residence in a tropical country suggested parasitic infection, malaria, tuberculosis or syphilis. Typhoid fever was also a possibility. In the first days of hospitalization the following additional diagnoses were considered: cyst of the liver, secondary to parasitic infection; aleukemic leukemia; Hodgkin's disease, and cirrhosis of the liver, secondary to splenomegaly of the Banti type.

The clinical course was puzzling. The severe diarrhea ceased, and the patient became constipated. There were persistent leukopenia and eosinophilia varying from 4 to 17 per cent. Urinalysis, examination of the stools and roentgenograms indicated nothing definite. Biopsy of an enlarged inguinal node showed chronic

inflammatory reactions. The blood, urine and stools did not show Bacillus typhosus. Finally, after several negative results of examination of the stools, ova of Schistosomum mansoni and Trichuris trichiura were found. There were eight ova of Schistosomum in twenty-five slides examined. On the following day ova of hookworm and Endamoeba coli and questionable Endamoeba histolytica were isolated. Ova of Schistosomum were then reported with some regularity, so treatment with antimony and potassium tartrate was instituted. This was given in doses of ¼ grain (0.016 Gm.) intravenously every second day for four doses. There being no untoward reaction, the dose was increased to ½ grain (0.03 Gm.) every second day until a total of 10 grains (0.64 Gm.) had been given. The ova of Schistosomum gradually decreased in number and finally disappeared. However, one month after treatment was completed ova reappeared. During this time the patient's general condition improved greatly; the red cell count and hemoglobin rose slightly, but the white cell count remained between 4,000 and 5,000, and the eosinophils varied between 4 and 17 per cent, with an average of 10 per cent. Three months after admission the patient was discharged to a convalescent home in Westchester.

Nine days later she complained of cough, headache and vomiting. The temperature was 104 F. Her condition became progressively worse, and she was referred back to St. Vincent's Hospital for further treatment.

On admission she had a temperature of 106 F., with a definite pneumonia of the lower lobe of the right lung. The white blood count was only 6,450, with 60 per cent polymorphonuclears, 24 per cent lymphocytes and 12 per cent eosinophils. The pneumonic process extended from the lower to the middle lobe of the right lung and then to the lower lobe of the left lung. Her condition became grave. A week later signs of fluid developed at the base of the right lung. For the first time the white cell count rose to 21,600.

The patient complained of abdominal pain. The abdomen, which had always been distended, was more so now, and signs of peritonitis appeared. Coincidentally with this, fluid appeared in the left side of the chest, to be followed within a few days by the appearance of fluid in the right side of the chest. The patient was dying. Cyanosis and dyspnea were marked. To relieve respiratory embarrassment abdominal paracentesis was performed, and more than 1,500 cc. of viscid, greenish-yellow pus was obtained. Type I Pneumococcus was recovered. There were no ova or parasites. Her condition improved somewhat, but the abdomen refilled. Four days later the patient experienced a spontaneous abdominal perforation, the site of rupture being in the midline above the umbilicus and not at the site of the previous aspiration. Between 1,500 and 2,000 cc. of pus was released. Following repeated transfusions and the administration of pneumococcic antiserum, her general condition gradually improved. One month later, when her condition was fair, resection of ribs was performed on the right. The response was satisfactory, and two weeks later thoracotomy of the left side of the chest was performed. Type I Pneumococcus was recovered from each empyema cavity. Both pleural cavities and the peritoneal cavity gradually cleared. However, diastasis recti abdominis developed at the site of the spontaneous abdominal perforation, and at the time of discharge was about 10 cm. in width. Because of her weakened condition, surgical intervention was to be deferred for about six months.

Toward the end of her illness, ova of Schistosomum manonsi again appeared in the stools, and treatment with antimony and potassium tartrate was again instituted. She was discharged on March 4, 1934, in good health and is now being followed in the outpatient department of St. Vincent's Hospital.

Hospital records indicate that infestation with Schistosomum mansoni is unusual in the vicinity of New York City. However, when one realizes that Schistosomum mansoni disease is endemic in Puerto Rico and that there are between 50,000 and 60,000 native-born Puerto Ricans now living in New York City, it is evident that many cases must escape one's notice. In one hospital only three cases have been diagnosed within the last three years, during which time the admissions have totaled approximately 50,000. All these cases occurred in Puerto Ricans.

We believe that all vague gastro-intestinal disorders in patients who have lived in the tropics should be investigated from the point of view of parasitic infection. and that infestation with Schistosomum mansoni should be especially considered in those who have lived in Puerto Rico.

PICK'S DISEASE IN A TWELVE YEAR OLD BOY. DR. JACOB L. ROTHSTEIN.

W. N., a 12 year old boy, was admitted to the Lenox Hill Hospital a year ago because of swelling of the abdomen of six months' duration and vague, intermittent pains in the muscles and joints of one years' duration. For one week prior to admission dyspnea on exertion, orthopnea and slight cyanosis had developed. Pain in the precordial region, palpitation or swelling of the extremities had never been noted. The patient had never had any attacks of acute rheumatic fever, chorea, definite arthritis or severe sore throat.

Save for measles at 2 years of age, the boy had been well. Birth, feeding and development had been normal. The family history is without significance, and the child has never been exposed to tuberculosis.

Physical examination on admission revealed: evidences of a pleural effusion at the base of the right lung posteriorly; slight enlargement of the heart to the right; an apical systolic murmur, but no interspatial retractions; pleuropericardial rubs along the right sternal margin; marked ascites; an enlarged liver and spleen; dyspnea; orthopnea, and cyanosis of the lips and nail beds. Extremital edema was not present.

The blood count, sedimentation time, icteric index and blood chemistry were normal. Urinalysis revealed albumin (1+), and a few leukocytes and epithelial cells were seen on microscopic examination. The Pirquet test and the Mantoux test with 0.1 mg. of tuberculin gave negative results. The Wassermann reaction was negative with both antigens.

Abdominal paracentesis was performed on the third day, and 5,300 cc. of an amber, slightly turbid fluid was removed, the abdominal circumference measuring 15 cm. less following the tap. The fluid was sterile on culture and contained 200 leukocytes per cubic millimeter, with lymphocytes predominating. A specimen was injected intraperitoneally into a guinea-pig, but autopsy two months later did not reveal any evidence of tuberculosis.

On roentgen examination the cardiac shadow was somewhat increased, with a bulging left lateral border, and a small pleural effusion was present in the right costophrenic angle. On repeated fluoroscopic examination the auricular and ventricular contractions were observed to be lessened and undulatory, but no tug of the diaphragm or fixation of the lung at the height of inspiration was seen. An electrocardiogram revealed fixation of the electrical axis of the heart in all leads on shift position. Repeated venous pressures taken by the method of Eyster revealed a heightened level of 200 mm. of physiologic solution of sodium chloride. The vital capacity was definitely diminished.

The child remained free from symptoms following the abnormal paracentesis. The pleuropericardial rubs were no longer heard at the end of the third week. A small amount of ascitic fluid gradually reaccumulated without embarrassing the child. The liver and spleen remained the same size throughout his two months' stay in the hospital. On the day prior to discharge fluoroscopic examination revealed the ventricular and auricular pulsations to be much more nearly normal than before. Since his discharge the child has remained relatively well, save for slight dyspnea on exertion. The venous pressure has remained persistently elevated.

A tentative diagnosis of Pick's disease had been made originally in this case, based on the slow onset, the history of probable rheumatic manifestations (pains in the muscles and joints), the increasingly marked ascites with complete absence of extremital edema and the paucity of cardiac signs in proportion to the evidences of marked circulatory embarrassment (engorged liver and spleen, ascites, effusion of the pleura of the right lung, cyanosis and dyspnea). The diagnosis has been

substantiated by the further findings of: (1) heightened venous pressure; (2) fixation of the electrical axis of the heart on shift of position, as evidence on the electrocardiogram, and (3) the abnormally lessened, undulatory ventricular and auricular pulsations observed fluoroscopically. Pericardiectomy was advised as affording the best chance for permanent relief, but was not performed because of parental opposition.

DISCUSSION

DR. F. ELMER JOHNSON: What was the etiology in this case?

DR. JACOB L. ROTHSTEIN: The etiologic agent in this case was probably rheumatic. Although the child had never had a definite attack of acute rheumatic fever, arthritis, severe sore throat or chorea, the history of vague pains in the muscles and joints for one year prior to hospitalization must be regarded as suggestive of rheumatic infection. During the course of the investigation at the Lenox Hill Hospital we were never able to demonstrate any evidence of a tuberculous infection. The Pirquet and Mantoux tests both gave negative results. A specimen of the fluid obtained by abdominal puncture was injected intraperitoneally into a guinea-pig, but on autopsy two months later no evidence of tuberculosis was found. In a recent survey of the literature I collected a series of thirty-four instances of adherent pericardium in children on whom pericardiectomy was performed; in about 60 per cent of these cases the etiologic factor was rheumatic, whereas in only 33 per cent was a tuberculous basis present.

DR. RUSSELL B. SCOBIE: A Puerto Rican girl, now 3 years old, was first admitted to St. Luke's Hospital fifteen months ago (in February 1933). The Mantoux test gave a strongly positive reaction, and roentgenograms showed an enlarged cardiac shadow consistent with pericardial effusion. During the patient's stay seven different observers heard a pericardial friction rub. There were no murmurs, and the question of tuberculous pericarditis was raised. Abdominal examination gave negative results. There have been eight admissions to date. At present the enlarged abdomen with fluid wave is the striking clinical feature. There had never been any peripheral edema. From the reports that I followed I was led to believe that more cases of this kind had a tuberculous basis. At the Massachusetts General Hospital three autopsies showed a pathologic condition consistent with tuberculosis, though no tuberculous lesion had been demonstrated clinically. They believe that the etiology of Pick's disease is not on a rheumatic basis. Two of their five patients on whom pericardiectomy was performed (40 per cent) died. The question of the etiology is still an open point.

DR. JACOB L. ROTHSTEIN: I must again emphasize that the series which I referred to consisted only of cases of adherent pericardium in children on whom pericardiectomy had been performed. It may be coincidental that analysis of the data offered in the individual reports of these cases concerning the course and the investigation revealed rheumatic fever to be almost twice as common as tuberculosis as the etiologic agent for the pericardial adhesions.

I should like to emphasize an additional point in the diagnosis of Pick's disease. I believe that two factors must be present to substantiate the clinical diagnosis—(1) an elevated venous pressure and (2) fixation of the electrical axis of the heart on the electrocardiogram with change of position. Another point of interest is that extremital edema may or may not be present, for it results only mechanically from the effect of the pressure of a large amount of ascitic fluid on the iliac veins. If the pressure is not great enough, no extremital edema is present. In conclusion, it is my opinion that the only possible chance for a permanent cure is that afforded by surgical rather than medical measures. Sooner or later, perhaps within one or two years, this patient may succumb either to the underlying disease process which caused the pericarditis or to the circulatory failure resulting from the constriction of the heart by the scarred pericardium. If surgical intervention is permitted and carried out, one at least relieves the heart of the mechanical strain under which it has been laboring.

DR. RUSSELL B. SCOBIE: This syndrome can be produced in dogs by injecting from 50 to 100 cc. of surgical solution of chlorinated soda (Dakin's solution) into the pericardial sac. Chronic fibrous adhesions in the region of the liver are found in the dogs, as have been described in the records of patients who had died of Pick's disease.

AMYOTONIA CONGENITA. DR. HERBERT F. JACKSON.

An infant, 7 weeks old at the time of death, was admitted to St. Luke's Hospital when he was 8 days old. The father and mother are living and well. One other child, 6 years old, is living and well. One year ago the mother gave birth to an infant who showed symptoms and signs of Oppenheim's disease immediately after birth and who lived only a short time.

The infant showed all the characteristic signs and symptoms of Oppenheim's disease, or amyotonia congenita; this was easily recognizable at birth. He lay in any position that he was placed in, completely helpless and motionless. His cry was weak, and at times he became very cyanotic. The knee jerks were absent, but sensation was present. Breathing was almost completely abdominal, there being only ¼ inch (0.64 cm.) excursion in the wall of the chest during respiration. He took his food fairly well, having better powers of sucking than most infants of this type, and his weight increased from 8 pounds and 10½ ounces (3,926.4 Gm.) on admission to 10 pounds and 1 ounce (4,564.3 Gm.)

A piece of muscle which was excised showed the typical pale, porklike appearance associated with this disease. The pathologic report on the excised muscle was as follows: The muscle tissue was pale. A section showed characteristic diminution in the size of the muscle fibers without any inflammatory lesion. The connective tissue cells of the fascia were large in comparison with the minute nuclei. Nerve endings were few, and those present had undergone myxomatous degeneration.

The blood showed 80 per cent hemoglobin; 4,100,000 red cells and 13,300 white cells, with 30 per cent neutrophils, 62 per cent lymphocytes, 6 per cent transitionals and 2 per cent eosinophils. The morphologic features were normal. All other laboratory determinations were normal.

Unfortunately, the patient died the night before the meeting. There are two points about this case which make it interesting. First, there is a definite history of two children in the same family with amyotonia congenita. One died a year ago at the age of 4 months. There is one child living, 6 years old, who is perfectly normal. The second point of interest is the easy recognition of this condition, even at birth, as the baby showed the typical weakness and paralysis as soon as he was born.

ERYTHEMA NODOSUM: A LINK IN A RHEUMATIC SYNDROME. DR. IRVING A. CLAMAN.

A colored girl, 7 years old, was admitted to the Hospital for Joint Diseases on Jan. 15, 1934. She complained of severe pain in the right hip, with tenderness of three days' duration. The temperature was 102 F. She was unable to bear weight on her right leg and kept the right hip flexed. Any attempt to straighten the thigh was distinctly painful. No other joints were involved. The past history was unimportant. A diagnosis of suppurative arthritis of the right hip was made. A roentgenogram at this time showed no abnormality.

On physical examination the patient appeared acutely ill and was suffering pain referred to the right hip. The tonsils were enlarged and moderately inflamed. The cervical lymphatic glands were palpable. The heart's point of maximal impulse was in the fifth interspace in the midclavicular line. A short, soft, blowing systolic murmur was heard over this area. The height of the patient was 51 inches (129.5 cm.), and the weight was 44 pounds (20 Kg.). The temperature was 102 F.

The patient was unable to sit, stand or walk because of the pain in the right hip. The leg was externally rotated, and there were tenderness on pressure over

the joint of the hip and marked limitation due to muscular spasm. The extremity was put up in Buck's extension traction. The pain in the right hip continued for two days. Thirty grains (1.9 Gm.) of sodium salicylate and an equal amount of sodium bicarbonate were given daily. The next day spasm and pain in the right hip diminished considerably under the traction, and the symptoms appeared in the left hip. The temperature remained 102 F. In view of the shifting signs from one joint to another, the diagnosis of acute rheumatic fever was made.

On the second day after admission the temperature dropped to 100 F.; the child was markedly improved symptomatically and was free from pain. She sat up easily. Pressure over both hips was not painful, and traction was removed. The dose of salicylates was decreased to 20 grains (1.29 Gm.) daily and was discontinued eight days after admission.

The red blood cell count was 4,000,000 on admission, with hemoglobin 65 per cent. White cells numbered 12,000, with 63 per cent polymorphonuclears. One month later the red cell count had risen to 4,650,000. The Mantoux test with a 1:10,000 solution of tuberculin gave a negative result. The temperature rose to 103 F. and remained between 102 and 103 F. for two weeks.

Three days after the onset of the fever typical lesions of erythema nodosum appeared on the anterior surfaces of both legs and extended about 6 inches (15.24 cm.) above the knees. Three days after this there was an acute rheumatic condition of the left wrist. The Mantoux test with a 1:1,000 solution of tuberculin was strongly positive with both human and bovine tuberculin. The erythema nodosum disappeared within nine days, and three days later typical moderate choreiform movement were noted in all the extremities and in the face. For one week prior to this time 40 grains (2.59 Gm.) of salicylates were given daily. Gastric lavage showed no tubercle bacilli on two occasions. Guinea-pigs were inoculated both times, with negative results. The systolic murmur became more marked and was transmitted to the anterior axillary line. A roentgenogram of the heart showed no gross abnormality. Electrocardiograms were normal on two occasions. Three daily doses of typhoid-paratyphoid vaccine (0.05, 0.1 and 0.1 cc., respectively), were given, with good reactions. There was no lighting up of the rheumatic condition of any joint after this treatment. Treatment with phenobarbital in doses of 0.5 grain (0.032 Gm.) three times a day was begun and was continued for two weeks, at the end of which time the chorea had entirely disappeared. Two weeks after the onset of the chorea rheumatic nodules were seen on the ninth and tenth dorsal vertebrae. These disappeared within ten days. On discharge, four months after admission, the child weighed 45½ pounds (20.6 Kg.). The weight at admission had been 44 pounds (20 Kg.). The temperature was normal for one month. A systolic murmur was present at the apex of the heart.

This case is of interest because of monarticular involvement at the onset of acute rheumatic fever, followed by typical lesions of erythema nodosum. Intradermal injections of tuberculin made during the first acute rheumatic fever gave negative results. With the appearance of the erythema nodosum the reaction to the Mantoux test became strongly positive. Repeated tests gave positive results. Rheumatic cardiac disease was present from the onset of the present illness and did not become worse. Chorea then developed. Injections of typhoid-paratyphoid vaccine did not bring about any recurrence of the rheumatic manifestations. Finally, rheumatic nodules appeared with the subsidence of the chorea. The erythema nodosum in this case appeared to be a link in a definite rheumatic syndrome.

CHRONIC THROMBOSIS OF THE SPLENIC VEIN. DR. HARRY M. GREENWALD.

B. F., a girl, 2½ years old, was brought to my office on Nov. 1, 1933, because of a severe gastric hemorrhage which had occurred the night before.

The father was suffering from tuberculosis, and the mother was under treatment for chronic cardiac disease; two brothers were living and well. The past history was not significant.

On October 28 the child complained of abdominal pain and refused food; the following day, however, she appeared well. Three days later she vomited her breakfast and again refused all food for the remainder of the day. At 8 p. m. she had a profuse hemorrhage from the mouth; the bleeding occurred suddenly and was not accompanied or preceded by either vomiting or coughing. The temperature was not elevated, and there was no complaint of pain. The child became pale immediately after the hemorrhage. The next day she was brought to my office, where physical examination revealed the following (only the essential findings are given): The sensorium was clear, and the nutritional status was good. There was marked pallor of the skin. The mucous membranes of the conjunctiva and mouth were pale; petechiae and hemorrhages were not seen. Physical and fluoroscopic examinations of the lungs gave negative results. The abdomen was large and protuberant, and there was dilatation of the superficial veins of the lower part of the anterior surface of the thorax and the upper portion of the abdomen. The spleen could be felt three fingerbreadths below the costal margin; there was no enlargement, however, of any of the lymphatic glands. The capillary resistance test gave negative results. Estimation of the hemoglobin (Sahli) showed 20 per cent. The white blood cell count showed 3,800 cells, with a preponderance of lymphocytes. A diagnosis of thrombosis of the splenic vein was made.

The patient was admitted to the Israel Zion Hospital on the afternoon of the same day. Examination of the blood at the hospital showed 1,900,000 red blood cells and 22 per cent hemoglobin (Sahli). The white blood cells numbered 4,200, of which 41 per cent were neutrophils, 51 per cent lymphocytes and 2 per cent myelocytes. The bleeding and coagulation times were normal, and the platelet count was 260,000. Two hundred cubic centimeters of whole blood was given directly into the vein. The transfusion was given, for two purposes: first, to relieve the severe secondary anemia which had resulted from the hemorrhage and, second, to see whether rapid increase in the size of the spleen would take place. This proved to be the case, for the spleen could be felt four fingerbreadths below the costal margin on the following day. This was considered important confirmatory evidence in favor of the diagnosis.

On November 5 a blood count showed 2,350,000 red cells and 4,100 white cells, of which 56 per cent were neutrophils, 42 per cent lymphocytes and 2 per cent monocytes. The hemoglobin content was 49 per cent (Sahli). The presence of leukopenia, even after a severe hemorrhage, and its persistence after transfusion were considered additional confirmatory findings. On this day surgical intervention was advised, and it was suggested that ligation of the splenic vessels be performed instead of splenectomy. This procedure seemed logical for two reasons: 1. No pathologic changes, as a rule, are present in the spleen early in the disease; the changes that occur later result from the chronic stasis which is always present in this condition; therefore, early removal of the spleen is unnecessary. 2. To prevent future hemorrhages it is necessary to divert the circulation from the spleen; this can be accomplished as effectively by ligation as by splenectomy and with a great deal less risk to the patient. Hemorrhages occur in chronic thrombosis of the splenic vein as a result of rupture of esophageal and gastric varices, when overfilling of the collateral veins occurs.

Obviously, if the portal circulation is also obstructed or interfered with because of concomitant thrombosis, sclerosis or congenital anomaly of the portal vein, splenectomy or ligation of the splenic vessels will fail to produce the desired result.

On November 6 the child was operated on. A small amount of serosanguineous fluid was found free in the abdominal cavity. The splenic vein was thrombosed from the spleen to the greater curvature of the stomach. The vessels were ligated, and the wound was closed. The following day the temperature became elevated and there were evidences of a pneumonic process at the base of the left lung; the child, however, did not look very ill. The elevation of temperature persisted for several weeks. The child finally recovered after a prolonged convalescence.

Examination of the blood on the day following the operation showed 2,900,000 red cells; 10,000 white cells, with 79 per cent polymorphonuclears, and a hemoglobin content of 47 per cent. Examination of the blood eleven weeks after the operation showed 3,100,000 red cells and 6,000 white cells, with 29 per cent neutrophils, 67 per cent lymphocytes and 4 per cent myelocytes. The hemoglobin content was 65 per cent and the platelet count 300,000. The bleeding time was three minutes and the coagulation time seven minutes. In other words, leukopenia, with a preponderance of lymphocytes, was again in evidence. The spleen was no longer palpable.

It should be emphasized that splenectomy is contraindicated if the thrombosis has extended to the portal vein. The presence of ascites, venectasia, abnormal changes in the size of the liver and diarrhea should lead one to suspect involvement of this vein.

The future of a patient with this disease is doubtful, for, as Walgren stated, "He is walking on a volcano." The prognosis should always be made with the greatest caution, because dangerous symptoms have been known to develop even after twenty years of apparent good health. Whether a patient can be cured without operation is impossible to say, because of the great difficulty of making an exact diagnosis.

This case is of interest for several reasons: First, this patient is probably the youngest child (2½ years old) in whom severe gastric hemorrhage has occurred. In 1930 van Creveld reported a case of anomaly of the portal vein with gastric hemorrhages in a child 4 years old. He stated at that time that, so far as he knew, this was the youngest patient in whom severe gastric hemorrhage had been observed. Second, the correct diagnosis was made preoperatively and comparatively early. Third, the thrombosis of the splenic vein was evident at the time of operation. Although a number of cases of splenomegaly and gastric hemorrhage have been reported in the literature under the title of "Thrombosis of the Splenic Vein," thrombosis has been demonstrated in but few instances. Fourth, there was a departure from the orthodox method of treatment; that is, ligation of the vessels was done instead of splenectomy. In these cases the gastric hemorrhage is due to rupture of varices which result from undue strain on the collateral circulation in an effort to remove the venous blood from the spleen. To prevent subsequent gastric hemorrhage it is, therefore, necessary only to divert the circulation from the spleen, and this can be accomplished as effectively by ligation as by splenectomy and with less risk to the patient. It must be remembered, however, that if the process also involves the portal vein no benefit need be expected from ligation of the splenic vessels. The presence of changes in the size of the liver, ascites, diarrhea and marked venectasia, particularly on the right side, are indications that the portal vein is affected.

So far as the diagnosis is concerned, if a child is seen who has had a severe gastric hemorrhage and if a moderate increase in the size of the spleen is observed, thrombosis of the splenic vein should be suspected. If reliable information is obtained that the spleen was larger before the hemorrhage, if it increases in size again several days after the bleeding and if, in addition, moderate anemia with persistent leukopenia is present, one can be reasonably certain that one is dealing with thrombosis of the splenic vein. The disease should be differentiated from gastric ulcer, Gaucher's disease, thrombocytopenic purpura and tuberculosis of the spleen.

DISCUSSION

The question was asked whether partial or complete ligation was performed.

DR. HARRY M. GREENWALD: Complete ligation was done.

DR. JOHN CAFFEY: Were varices in the stomach demonstrated by roentgenograms?

DR. HARRY M. GREENWALD: We did not attempt to demonstrate the varices, for we understood that they were there.

RHEUMATIC ENCEPHALITIS (CHOREA INSANIENS); AVERTIN THERAPY. DR. IRVING A. FRISCH.

S. J., a girl, aged 11½ years, nine days prior to admission to Beth Israel Hospital had an acute infection of the upper respiratory tract, followed on the fourth day by painful swellings of the joints of the wrists and ankles.

Four years previously she had measles followed by a mild attack of polyarthritis, and two years ago scarlet fever associated with slightly swollen and painful joints. Otherwise she had always been well. There were no rheumatic manifestations.

Examination on admission showed a temperature of 104 F. There was tenderness about the ankles and wrists and the small joints of the hands, with moderate limitation of motion. The heart rate was rapid and regular; there was a systolic murmur at the apex of the heart, which was not transmitted. A teleroentgenogram showed no cardiac enlargement. An electrocardiogram showed inverted T waves in leads I and II: these changes were interpreted as being due to myocardial involvement. (No digitalis had been given.) The sedimentation rate was 90 mm. in forty-five minutes (10 mm. being the upper limit of normal). White blood cells numbered 18,000, with 88 per cent polymorphonuclear cells. The diagnosis at the time of admission was acute rheumatic fever of the polyarthritic type.

Rapid improvement of all the symptoms occurred under salicylate therapy. By the end of the first week the temperature was normal and the pains and swellings in the joints had disappeared.

The onset of chorea occurred on the twelfth day after admission to the hospital. There was a rapid increase in the severity of the symptoms, so that five days after the onset of this condition the child was maniac and motor activities were extremely violent. The temperature was up to 105 F., and the child was on the verge of collapse from exhaustion. Marked toxic erythema, with hemorrhagic spots on the abdomen and thighs, was present. A blood culture was sterile. Ordinary sedatives (barbital group) and morphine had no effect on controlling the condition. Avertin —a nonvolatile anesthetic—was then given by rectum in a dose of 80 mg. per kilogram of body weight. The results were remarkable: The child fell asleep within twenty minutes and was quiet for eight hours, during which fluids could be administered by mouth and by hypodermoclysis. As the avertin wore off, paraldehyde (5 cc. by rectum) continued this effect to a moderate extent. This course of avertin and paraldehyde was continued throughout the second week, during which time the patient's temperature ranged between 103 and 106 F. daily.

The condition of the heart was interesting, a definite pericardial friction rub being noted at this time. An electrocardiogram showed partial heart block (the P R interval was twenty-eight hundredths of a second). Because of the hyperpyrexia and the rheumatic involvement, large doses of salicylates were administered, with no apparent effect. On the twelfth day of her illness, after she had received 200 grains (12.9 Gm.) of sodium salicylate within the past forty-eight hours, the temperature rose to 108.4 F., and the child was semicomatose. Marked cyanosis was present. Examination of the blood for methemoglobin gave negative results. A roentgenogram of the chest showed nothing abnormal, except beginning pericardial effusion. There was no evidence of cardiac decompensation. A second blood culture was sterile. Spinal tap at this time showed fluid under slightly increased pressure, globulin (1 +), a normal sugar content and 70 cells per cubic millimeter, 80 per cent of which were lymphocytes.

There was some improvement in the chorea during the third week. The temperature ranged lower (from 102 to 104 F.), and the movements were less marked. The child was semicomatose, and nutrition was maintained by means of transfusion and hypodermoclysis. Marked pericardial effusion, but no circulatory embarrassment, was present. Definite but slow improvement continued, so that by the end of the fourth week choreiform movements were mild and there was a slight response to commands. This response was associated with a peculiar facial grimace, and paralysis of the right side of the face was also present. By

the middle of the fifth week all choreiform movements had ceased. The child had a fixed facial expression, and the eyes were held in a rigid downward stare, with inability for ocular motor activity in any direction. Definite emotional instability and a bilateral Babinski sign, with hyperactive deep reflexes, were also present. The opinion of neurologists was that this condition resulted from widespread encephalitis which most markedly involved the basal ganglions.

The further course was one of slow but gradual improvement. The fixed facial expression disappeared during the eighth week, and the ocular motor movements returned to normal by the end of the ninth week. During this time the pericardial effusion was also slowly absorbed. On discharge from the hospital four months after the onset of the chorea the child seemed perfectly well, and there was only a soft systolic murmur at the apex of the heart, with no cardiac enlargement.

DISCUSSION

DR. IRVING A. FRISCH: This was a case of the most severe type of Sydenham's chorea, characterized by marked involvement of the central nervous system, as was evidenced by the wild motor activity, the severe emotional outburst and the hyperpyrexia. During the course of this condition heart block and pericardial effusion developed. Most interesting were the postchoreiform phenomena. These consisted of a rigid facies and inability for ocular motor activity, the eyes being held in a fixed downward stare. In view of the more recent knowledge of the pathology of chorea, the marked involvement of the central nervous system in this case and the close relationship of the latter to the virus of rheumatic fever, it seemed logical to designate this case as one of rheumatic encephalitis rather than to use the older term "chorea insaniens."

In these cases there is a high mortality, death, if not due to toxemia, being usually caused by the marked motor activity in combination with the high temperature and lack of nourishment. In this case the use of avertin produced a quieting effect after other hypnotics failed, and during the course of this anesthesia one was able to administer nourishment and other therapeutic aids. This is worth trying in similar cases.

DR. F. ELMER JOHNSON: What does the "rapid improvement of all symptoms under salicylate treatment" mean?

DR. IRVING A. FRISCH: This refers to the earlier period. The child entered the hospital with a simple case of acute rheumatic fever of nine days' duration. The temperature was 104 F., and there was multiple involvement. The pains in the joints and the fever rapidly cleared up under salicylate therapy, so that at the end of one week the temperature was normal and all other symptoms had disappeared. The chorea began five days after this. Salicylates had no apparent effect on the second part of this disease. In fact, shortly after the administration of 120 grains (7.7 Gm.) daily, the temperature rose to 108.4 F.

LEUKEMIA WITH EXTENSIVE OSSEOUS CHANGES, SIMULATING RHEUMATIC FEVER. DR. LUCY PORTER SUTTON.

D. O'C., a white girl, aged 2 years and 8 months, was first admitted to Bellevue Hospital in December 1929. The chief complaint was pain and swelling in the right forearm and wrist. There had been a similar condition in the left shoulder two months previously. The past history was irrelevant.

Physical examination showed a well developed girl who was not acutely ill; there was no fever. Superficial lymph nodes, including the right epitrochlear nodes, were palpable but not enlarged. The swelling of the right wrist was apparently connected not with the joint but with the lower end of the radius. There were limitation of movement at the wrist and wrist drop. Blood counts were normal, and the heart was normal. The report of the roentgen examination of the arm and wrists was that there were halisteresis of moderate degree and evidence of metaphysitis.

The diagnosis of rheumatic fever was suggested but not confirmed. The patient was discharged improved within 10 days.

On the second admission, six days after discharge, the chief complaint was pain and swelling in the left foot. Physical examination showed a temperature of 102 F., but the temperature was normal within ten days. The left ankle was hot, swollen and tender, and the left inguinal lymph nodes were enlarged. The heart was not enlarged or overacting, and there was no murmur or gallop. Otitis media developed later, with fever and enlarged cervical lymph nodes; the ear drained for several weeks. In blood counts the number of white cells ranged from 8,400 to 12,000, with a range of polymorphonuclears from 48 to 71 per cent. The hemoglobin was 75 per cent. Tonsillectomy was performed. The patient was discharged to a convalescent home in May.

The third admission was on June 24, 1930. In the interval the child had done well until three weeks previous to readmission, when fever and swollen ankles had developed. She was sent back from the home with the diagnosis of rheumatic fever. Physical examination revealed marked lymphadenopathy, especially of the cervical and femoral nodes. The left ankle was puffy and was red over the external malleolus. The heart was enlarged, and the heart rate was rapid. The liver and spleen were enlarged. On admission the diagnosis was Hodgkin's disease or lymphoid leukemia. Biopsy of a lymph node demonstrated lymphoid leukemia.

Other joints became involved at intervals. Hemorrhages from the bowel, into the skin and, shortly before death, from the gums, nose and ear occurred. Five transfusions and seven roentgen treatments were given, but the course was steadily downhill. Marked anemia developed. The hemoglobin was maintained at around 50 per cent, with a terminal drop to 20 per cent. The number of red cells dropped to 1,000,000. The number of white cells varied from 14,000 on admission to 19,000 (highest). The number of polymorphonuclears was reduced, and lymphocytes increased to more than 70 per cent. The number of platelets was reduced to 150,000 just before death. The blood count just before death was: red cells 1,000,000, with hemoglobin 20 per cent, and white cells 1,100, with polymorphonuclears 16 per cent, small lymphocytes 28 per cent, large lymphocytes 44 per cent and other forms 12 per cent. Death occurred on Jan. 2, 1931. Roentgenograms showed irregular atrophy of the long bones, which increased as the disease progressed.

DISCUSSION

DR. LUCY PORTER SUTTON: Our chief interest in this case was the diagnosis. For the first six months, except for tonsillitis, the joints were the outstanding feature. They were hot, tender, red and sore. The thing that kept us from making a diagnosis of rheumatic fever was the fact that the patient showed no involvement of the heart, and we believe that when rheumatic fever is present in patients under 3 years of age it affects the heart. The patient showed no symptoms on the basis of which we could make a definite diagnosis. The white cell counts were normal, and the white cells reacted in the presence of the acute infection by an increase in polymorphonuclears. The osseous changes were fairly characteristic, but were more extensive than in most cases of this kind.

DR. SAMUEL KARELITZ: Some years ago we had a case at Mount Sinai Hospital that answered closely to the description of this one. A 3 year old boy with a condition diagnosed as acute rheumatic fever, who had pains in the leg, was brought to the hospital. He had dactylitis of several of his fingers and some involvement of the wrist. Roentgenograms of the long bones showed periosteal changes, with moth-eaten areas in the cortex. Only after several months did we find some myelocytes in the blood stream. We suspected leukemia, which is what he had. Shortly after, we had an almost similar case, which turned out to be one of neuroblastoma. These children had cardiac murmurs, which were probably associated with the anemia. The pain in the joints and the dactylitis improved after transfusion, then recurred.

DR. K. K. MERRITT: We had a similar case at the Babies Hospital. An Italian girl, aged 4¾ years, had an illness of ten and one-half months' duration.

She had swelling of the right shoulder on admission, and a diagnosis of Still's disease was made. Subsequently, swelling of several joints of the fingers and of the joints of the left elbow developed. She had swelling and tenderness over several other bones, without evidence of definite articular involvement. A diagnosis of chronic lymphatic leukemia was made from the blood findings and from the characteristic osseous changes as shown by roentgenograms.

DR. JOHN CAFFEY: In this condition the proximal ends of the humeri have been involved earlier and more extensively than other bones. These ends are not examined as frequently in roentgenograms as other parts, and occasionally one slips up by not seeing the whole humerus.

NORTH PACIFIC PEDIATRIC SOCIETY

Midsummer Meeting, Vancouver, B. C., June 25, 1934

ARTHUR H. GRAY, M.D., *President, in the Chair*

ARMIN REMBE, M.D., *Vice-President*

R. H. SOMERS, M.D., *Secretary*

Morning Meeting

REPORT OF CASES. DR. G. O. MATTHEWS, Vancouver, B. C.

Cases are reported of 4 infants in the same family, the first dying at 6 months of age, the second at 10 weeks, the third at 4½ months and the fourth at 4½ months. All 4 cases terminated with bronchopneumonia preceded by a persistent cough. The family history, except for rheumatism in the father, is negative. The fourth baby had loose stools from the onset and at 2 weeks of age had a cough, as was stated by the mother, "just like the others." Physical examination gave entirely negative results, and roentgenograms of the chest were normal. At 6 weeks a cardiac murmur was noted. This was musical and to and fro in character. There was no cyanosis. The condition became gradually worse, and the child died at the age of 4½ months with terminal bronchopneumonia.

At autopsy the spleen and liver were normal. The lungs showed terminal bronchopneumonia. The heart was not enlarged, but the aorta was larger than normal. The aortic cusps were three times the normal thickness, and the foramen ovale was patent. The diagnosis was congenital aortic endocarditis. Microscopic examination showed fibrous thickening. The inference was that all four children had had congenitally diseased hearts.

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill.: One would expect the ductus arteriosis to have been patent.

DR. H. T. CLAY, Tacoma, Wash.: My experience has been that congenitally diseased hearts show decompensation as the requirements become greater.

DR. ARMIN REMBE, Seattle: In many cases of so-called thymic death one must consider the condition as congenital heart disease.

DR. G. O. MATTHEWS, Vancouver, B. C.: This was not a typical congenital condition of the heart, but probably fetal endocarditis.

A CASE FOR DIAGNOSIS. DR. J. H. B. GRANT, Vancouver, B. C.

A girl, 9 years old, is one of ten children; all the other children are alive and well. Her development has been normal; she has had several diseases of childhood. The abdomen had been larger than usual, as was reported by the mother,

for about two years. When she was first examined the heart beat was rapid, and the heart was considerably enlarged, with a murmur and thrill over the whole cardiac area. There was fluid in the abdomen, but no edema was present. The patient weighed 31 pounds (14.1 Kg.) at 7 years of age. The tuberculin reaction was repeatedly negative. The urine contained albumin (1 plus) and an occasional cast. The patient was hospitalized for three months in 1933. Following a severe cold the abdomen suddenly increased in size. Following scarlet fever she was readmitted to the hospital for examination a week ago. The heart was smaller than it had been two years before, but was still large. The liver was also smaller than it had been two years before. The weight of the patient was 41 pounds (18.6 Kg.), but most of the gain was due to fluid in the abdomen. Examination of the blood showed 13,000 white cells, with 78 per cent polymorphonuclears. Clear fluid of a specific gravity of 0.1012 was removed from the abdomen. A roentgenogram of the chest showed pleural effusion on the right side. Several diagnoses were considered: tumor, amyloid degeneration, tuberculosis, cirrhosis of the liver and passive congestion due to a congenitally diseased heart.

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill.: This case has been summed up as most physicians would have done. I would suggest a paracentesis of the chest as a further diagnostic procedure, since tuberculosis has been strongly suspected.

ACRODYNIA. DR. E. D. CARDER, Vancouver, B. C.

A girl, 15 months of age, has a normal developmental history; her weight was 32 pounds (14.5 Kg.) at the end of the year. She has never taken cod liver oil. At 1 year of age she had severe diarrhea and began to lose weight rapidly. Within two months she lost 12 pounds (5.4 Kg.). She was extremely irritable, slept poorly and had photophobia. The skin itched and the extremities were swollen, red, with desquamated skin. There was vomiting; the gums were swollen and inflamed, and one tooth was loosened. The usual treatment with sedatives and viosterol was given. At present the weight is 20 pounds (9.1 Kg.).

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill.: This seems to be a typical case of acrodynia. One does not see such cases as much in the Middle West as on the coast.

NEPHRITIS. DR. E. J. CURTIS, Vancouver, B. C.

A child, preceding hospitalization in 1932, had measles accompanied by rigidity of the neck and frontal headache. This was followed by purulent otitis media. Urinalysis showed large amount of albumin, with red cells. There was considerable edema. Drowsiness, coma and convulsions were treated by dehydration. Mastoidectomy was considered, but was not performed because of nephritis. There were red blood cells in the urine throughout this period. The blood showed nonprotein nitrogen, 60 mg. per hundred cubic centimeters. The blood pressure showed a change from 122 systolic and 82 diastolic to 130 systolic and 74 diastolic. A culture from the ear showed Streptococcus haemolyticus. The child has had a temperature for two years. Tuberculosis has been excluded. The specific gravity of the urine has varied from 1.02 to 1.03.

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill.: This child does not have chronic nephritis, because of the satisfactory specific gravity. There is a definite history of inflammatory disease. I should probably have recommended a mastoid operation, as nephritis is no contraindication.

DR. V. W. SPICKARD, Seattle: Should one carry out operative procedures, such as tonsillectomy, before the albuminuria has cleared up?

DR. A. H. SPOHN, Vancouver, B. C.: One should not take out the tonsils while the fever persists. Retinal changes at times have been found in patients with this condition in the Mayo Clinic.

DR. E. J. CURTIS, Vancouver, B. C.: This child had the tonsils and adenoids removed two years preceding the nephritis.

NEPHRITIS. DR. J. H. B. GRANT, Vancouver, B. C.

A girl, 12 years old, has had frequent tonsillitis. In 1932, she showed nephritis, but was well until 1933. At this time edema appeared, with blood and albumin in the urine. Later in the year the symptoms reappeared and persisted. She was hospitalized in February 1934 because of edema due to tonsillitis. The hemoglobin was 55 per cent, and she complained of dizziness. The heart was enlarged. Urinalysis showed a specific gravity of 0.1016 and albumin (2 plus), with many red cells and an occasional white cell and cast. She was kept in bed for one month. The edema disappeared. There was repeated epistaxis. Then tonsillectomy was performed. She has gained 12 pounds (5.4 Kg.) since leaving the hospital. There is no edema. The color is improved. The hemoglobin is 85 per cent, although the urine still shows albumin (2 plus), with an occasional red and white cell. The blood pressure is 112 systolic and 80 diastolic.

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill.: One does not know the condition of the urine before the illness. The patient is the victim of a chronic repeated inflammatory process. The epistaxis is not important. The prognosis in this case is good, as the specific gravity of the urine varies from 0.1008 to 0.1025.

DR. A. H. SPOHN, Vancouver, B. C.: Chilling is often followed by tonsillitis and aggravation of nephritis.

MULTIPLE ARTHRITIS WITH CONTRACTURES. DR. G. A. LAMONT, Vancouver, B. C.

A girl, 9 years old, has been ill for two years. Measles was followed by a nasal discharge, with swelling in two or three joints, which was followed in turn by fever. This infection resulted in pericardial effusion. The fluid was aspirated and found to be clear. A blood culture was sterile. Two weeks later the pericardium was aspirated again. There was a persistent elevation in temperature of from 100 to 101 F. Tonsillectomy was performed in an effort to remove all local infections. All the joints became large and painful. An effort was made to prevent contractures by orthopedic means, but the joints were too painful. The heart has remained entirely normal.

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill.: Active infection in the joints probably makes it unwise to attempt orthopedic measures.

DR. N. W. CLEIN, Seattle: This condition has some resemblance to Still's disease. Might the parathyroid supply be inadequate?

EWING'S TUMOR. DR. R. P. KINSMAN, Vancouver, B. C.

A boy, aged 7 years, received a bump on his head a year ago. A swelling resulted and did not disappear. There have been occasional vomiting and pain in the head. A tumor developed in the right temporal region. This was thought to be an old hematoma. The first roentgenograms appeared to be normal. A second series showed areas of rarefaction. Biopsy showed a tumor called endotheliomyeloma.

DISCUSSION

DR. E. J. CURTIS, Vancouver, B. C.: The tumor fluctuated in size. There were intermittent frontal headaches, which were becoming continuous, pain and elevation of the temperature to 100 F. The leukocyte count was up to 14,000. The long bones were more often affected, with metastases to the skull and lump.

DR. H. T. CLAY, Tacoma, Wash.: I have as a patient at present a Japanese boy with a Ewing's tumor of the femur of six or seven months' duration. Roentgen treatment has been of no value so far.

DR. C. A. ALDRICH, Winnetka, Ill.: One method of treatment which has not been mentioned is radical removal, resulting in 20 per cent cures.

CONGENITAL SYPHILIS. DR. E. J. CURTIS, Vancouver, B. C.

A child 2 years of age was admitted to the hospital with otitis media and bronchitis. No Kahn test was carried out at that time. Five months later he became irritable and had diarrhea. There were craniotabes, with rarefaction of the occiput, and also furunculosis. The Kahn reaction was three plus. The spleen was not enlarged. Facial paralysis developed with spasticity of the right arm and leg. Lumbar puncture showed 1,200 cells per hundred cubic centimeters. Treatment with acetarsone resulted in marked improvement within a short time. At the end of six months, however, examination of the serum still gave positive results. What I wish to know is whether treatment with acetarsone alone is adequate.

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill.: Treatment with acetarsone is being used a great deal. Babies under 1 year of age having nephritis die with ordinary treatment; under treatment with acetarsone, however, these children recover.

DR. N. W. CLEIN, Seattle: Roentgenograms of the long bones should be used in making the diagnosis and often show positive findings when examination of the serum gives negative results.

DR. ARMIN REMBE, Seattle: Should one treat babies of known syphilitic parents in whom the Wassermann reaction is negative?

DR. C. L. SMITH, Seattle: Is Dr. Curtis using mercury in conjunction with acetarsone? He will probably not get results unless he does.

DR. E. J. CURTIS, Vancouver, B. C.: One probably should use mercury. I advocate treating these babies early; one became extremely ill because treatment was delayed.

DIAPHRAGMATIC HERNIA. DR. A. H. SPOHN, Vancouver, B. C.

A child aged 14 months has eczema and malnutrition, with periodic vomiting and distress. It takes feedings easily. A roentgenogram showed complete absence of the right leaf of the diaphragm and a large amount of abdominal content in the chest. This case is probably not operable.

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill: I had one case in which operation for this condition was successful.

DR. H. H. SKINNER, Yakima, Wash.: I should like to cite the case of a 10 year old child who had as the only sign a persistent cough. A roentgenogram showed diaphragmatic hernia.

DR. H. E. COE, Seattle: In cases in which the condition cannot be demonstrated otherwise, giving an injection of barium sulphate and inverting the child will show a good picture.

STREPTOCOCCIC MENINGITIS. DR. J. R. DAVIES, Vancouver, B. C.

A child showing a slight cold on Saturday had a severe earache on Sunday. The drum was bulging and, when opened, popped loudly, with a resulting serosanguineous discharge. Forty-eight hours later the child became drowsy and vomited. There was no tenderness or swelling of the mastoid. A roentgenogram showed a cloudy mastoid. On operation the mastoid was entirely necrotic. A blood culture showed Streptococcus haemolyticus. Continuous spinal drainage was resorted to, with intermittent favorable progress.

DISCUSSION

DR. C. A. ALDRICH, Winnetka, Ill: Meningitis is one of the common causes of death. Three days is early for a mastoid to become necrotic. Meningitis is not the result of direct infection through the mastoid, unless infection takes place through the petrous portion. I should advise in addition to spinal drainage the use of convalescent streptococcic serum.

DR. FRANK H. DOUGLASS, Seattle: I suggest laminectomy, if necessary.

Afternoon Meeting

REPORT OF CASES. DR. C. A. ALDRICH, Winnetka, Ill.

Fourteen cases of scarlet fever are reported, each patient being a child whose life was in danger from overwhelming infection. The experimental work was done by Dr. Hoynes' use of convalescent scarlet fever serum. The mortality was 4.14 per cent, which is much lower than might have otherwise been expected.

DISCUSSION

DR. C. E. DOLMAN, the Connaught Laboratory, Toronto, Canada: There may be antibodies in patients who have had the disease that are not developed in animals from injections of a suspension of the serum. Convalescent serum is probably an improvement over ordinary laboratory serums.

DR. V. W. SPICKARD, Seattle: In a case of mastoid infection in a child, with extending cellulitis, blood was given from the mother, who had recently recovered from the same type of infection. Recovery was complete.

DR. H. H. SKINNER, Yakima, Wash: What is the manner of obtaining and preserving serum?

DR. C. A. ALDRICH, Winnetka, Ill.: The serum may be kept on ice for several months.

SUCTION DRAINAGE IN EMPYEMA. DR. W. M. PATON, Vancouver, B. C.

Ten cases are reported in which suction drainage was used from the onset and 4 cases in which it was used after failure of other methods. The average time spent in the hospital was thirty-one days. The average time for obliteration of the cavity was twenty-two days. An apparatus that I have devised was used in the treatment of these patients.

DISCUSSION

DR. H. E. COE, Seattle: For many years I favored open drainage. The pendulum is now swinging back to closed drainage. One should not use one method to the exclusion of all others. The treatment in each case should be carefully chosen.

SOME PHASES OF TUBERCULOSIS IN CHILDREN. DR. PERCY W. BARKER, Vancouver, B. C.

An effort is made to classify the various types of tuberculosis in childhood and to use the child material to locate cases resulting from contact in adults. Roent-

genograms demonstrating infantile, juvenile and adult types of tuberculosis and also nontuberculous infections resembling tuberculosis are shown.

DR. W. H. HATFIELD, Vancouver, B. C.: Physical examination is not satisfactory, and roentgenography and tuberculin tests are necessary. An effort is being made to reach patients with the adult type of tuberculosis through school children. Rest is absolutely essential in the treatment.

DR. ARMIN REMBE, Seattle: With the first infection the damage is done. There is an interval before susceptibility to reinfection. One should get at the tuberculosis in adults through the children.

DR. N. W. CLEIN, Seattle: Two hundred cases are reported from private practice, in 100 of which the condition is allergic and in 100 of which it is nonallergic. Seventy-eight per cent of the allergic cases developed in patients under 4 months of age. Skin tests and methods of elimination of food are used to determine susceptibility.

Book Reviews

Diet and Dental Health. By Milton T. Hanke. Price, $4. Pp. 236, with 22 plates and 63 graphs and tables. Chicago: University of Chicago Press, 1933.

This book is a report of a four year study by the Dental Research Club of Chicago, the author and other collaborators, which was carried out in the laboratories of the Otho A. Sprague Memorial Institute at the University of Chicago. Clinical observations were made on 500 patients sent to the investigators and 440 institutionalized children at Mooseheart, Ill. The latter group constituted material for the major study, which was divided into three periods: a control period, during which children were observed without altering conditions prevailing in the institution; a test period, in which certain of the previously observed children were given 16 ounces (473.18 cc.) of orange juice and the juice of one lemon daily, and a period of rechecking, in which only 3 ounces (88.7 cc.) of orange juice was administered in addition to the regular routine diet of the home. A detailed report of the findings at each examination of 341 children over the entire three year period at Mooseheart is furnished in an appendix. There is also included a rather elementary discussion of the dental tissues of man and a few of their common diseases, together with a more detailed consideration of the histopathology of scurvy in the guinea-pig.

The principal findings are as follows: With respect to studies of the guinea-pigs, 3 cc. (88.7 cc.) of orange juice daily was required to protect all animals from histologic evidence of scurvy. The changes in the dental pulp and dentine were considered to be specific and characteristic to the degree that they were suggested as "an excellent method for evaluating vitamin 'C' content of foodstuffs and experimental preparations." Orange juice that had stood for twenty-four hours in an open vessel was not found less effective than the freshly prepared material.

With respect to the patients studied individually and the children at Mooseheart, the administration of 16 ounces (473.18 cc.) of orange juice and one lemon daily was found materially to reduce gingival irritation, producing healthy gum tissue in most cases, and to affect dental caries favorably. There was observed in the Mooseheart group a striking effect on growth, which was apparently produced by the increased amounts of citrus fruit juice. The average gain in height and weight were commonly below the Baldwin standards in each year group (ages 11 to 18) during the control period. In the following period, with the administration of a pint (473.18 cc.) of orange juice and the juice of one lemon there was a marked increase in the rate of growth, so that the Baldwin standards were approximated. In the period of rechecking, when 3 ounces (88.7 cc.) of citrus fruit juice was given, the average gain in the year generally exceeded the standard.

The author believes that the American diet is sufficiently lacking in citrus fruit to permit the frequent recurrence of gingivitis and dental caries; that the addition of 3 ounces (88.7 cc.) of orange juice daily is not enough materially to affect these oral conditions and that "the administration of an adequate amount of citrus fruit juice to a diet that is nearly adequate in other respects reduces the intensity of the carious process, but does not completely remove the effects of the inherent tendency in all cases."

Mental Hygiene in the Community. By Clara Bassett. Price, $3.50. Pp. 394. New York: The Macmillan Company, 1934.

This is a comprehensive and intensive survey of the entire relationship of mental hygiene to community life. After a short introduction in which mental

hygiene is as well defined and explained as the reviewer has seen it done, there are chapters on mental hygiene and medicine; mental hygiene and nursing; mental hygiene and social service agencies; mental hygiene, delinquency and law; mental hygiene and parental education; mental hygiene and the preschool child; mental hygiene, education and the training of teachers; mental hygiene, the church and theological training; mental hygiene and industry; mental hygiene and recreation and mental hygiene and psychiatric institutions and agencies. Following each chapter is a comprehensive statement of suggestions for the investigation of these various subjects from the point of view of mental hygiene. This statement contains all the suggestions that one needs in the present stage of development of the science, if it can be called such, of mental hygiene. For example, among the suggestions for the investigation of the development of mental hygiene in schools of medicine there is a searching inquiry into the teaching of psychiatry in medical schools, and in this connection the question is asked as to the subordination of psychiatry to neurology.

Perhaps the most interesting chapter is that on education, with its appreciation of the changing trends in education and the suggestions for investigation at the end of the chapter. The only criticism the reviewer would make is as to whether the general note of belief in the curative action is overoptimistic. The chapter "Mental Hygiene, the Church and Theological Training" is handled in a way that expresses a realization of the force of belief. The pastor deals with troubles of the soul, and to the mentally distressed this may be more acceptable and more helpful than the medical approach, which insists on putting the blame on the body, if possible.

A careful reading of this book of three hundred and ninety-four pages may be boresome to many, but will certainly stimulate any one seriously interested by its wealth of detail and the searching questionnaires at the end of each chapter.

A suggestive bibliography and an index complete the book.

La tuberculose pulmonaire et les maladies de l'appareil respiratoire de l'enfant et de l'adolescent. In 2 volumes. By P. F. Armand-DeLille, Ch. Lestocquoy and Réné Huguenin. Pp. 493, with 352 illustrations. Paris: Amédée LeGrand, 1933.

One is so overwhelmed on looking over these two volumes that description seems commonplace. Nothing approaching them has ever been seen by the reviewer. The first volume and a large part of the second are taken up with the description of tuberculosis in infancy, childhood and adolescence. The scheme followed is to show the roentgenogram with a schematic explanation and, where possible, the pathologic specimen presented in such a way as to conform in a large measure to the picture in the roentgenogram. In addition a short résumé of the case is given with each of these pictures. The size of the page makes it possible to show the roentgenogram in life size or almost in life size, so that the explanations are peculiarly striking.

In addition to tuberculosis in childhood, which is considered from every angle and in every form, the authors take up other conditions in the chest: acute infections, lobar pneumonia and bronchopneumonia, serofibrinous pleurisy, empyema and tumors.

The material is excellently presented and amply illustrated, as is shown by the fact that there are four hundred and ninety-three pages and three hundred and fifty-two illustrations. However, the illustrations are frequently double, so that there is at least probably one to a page on the average. The text, especially that on tuberculosis, is clear and succinct and is comprehensive, as would be expected from such authors, whose knowledge of the subject is probably at least as great as that of any one in the world today.

Let's Talk About Your Baby. By H. Kent Tenney Jr., M.D. Price, $1.50. Pp. 71. Madison, Wis.: Milgore Printing Company, 1934.

As the title suggests, this book is something different. Without being flippant, one can say that it is a chatty book. It conveys in a conversational manner to the mother and, incidentally, to the physician many of the things which both should know. It is evidently material which has been culled from experience and contains an amount of hard common sense that one would scarcely expect to find in so small a volume. It can be recommended to any mother and to any physician who has to care for babies. It will save the former much anxiety and will relieve the latter of much attention to details unimportant to him but of supreme importance to his patients. Altogether, this is an excellent book.

Chirurgie infantile d'urgence. By M. Fèvre. Price, 70 francs. Pp. 449, with 109 figures. Paris: Masson & Cie, 1933.

The entire field of emergency operative procedures in infants is covered in this volume. The emphasis is placed on the clinical signs and the technic of treatment. Preoperative and postoperative measures are described in detail. There are numerous drawings, reproductions of photographs and histories of cases. The technic of the various operations is clearly and concisely described.

The first chapter deals with general surgical considerations in infants, such as medical management and the choice of anesthetic. The remainder of the book is divided into chapters, each dealing with the surgery of one particular part or system of the body, such as the head and face, neck, thorax, abdomen and gastro-intestinal tract, genito-urinary system, extremities and congenital malformations. There is one chapter on infections and burns.

The contents of the book are based on the author's seven years of clinical experience in the service of the "Enfants Malades" under the direction of Professeur Ombrédanne. Surgeons who are called on to perform emergency operative work on infants should find a great deal of practical value in this book.

The Anemias. By Janet M. Vaughan. Price, $4. Pp. 248, with 24 illustrations. London: Oxford Medical Publications, 1934.

The first chapter of this book deals with normal erythropoiesis, of the anatomy of which Prof. H. M. Turnbull contributed an interesting description. The successive chapters take up the author's classification of the anemias, which are as follows: (1) dyshemopoietic anemias caused by deficiency such as lack of iron, of pernicious anemia factor, of vitamin C and of thyroxine. Classified under the same group are toxic dyshemopoietic anemias and unexplained dyshemopoietic anemias, such as osteosclerosis, Cooley's anemia, and erthroblastosis fetalis; (2) the posthemorrhagic anemias, and (3) the hemolytic anemias. Lastly are grouped the unclassified anemias, such as Banti's disease and von Jaksch's anemia.

Each of these conditions is discussed in a systematic manner as to etiology, pathology, differential diagnosis and treatment. The descriptions are lucid and readable. The illustrations are excellent, and the binding and paper are well in keeping with the Oxford standard. The author has presented an excellent résumé of the anemias as known today. The various theories and differences of opinion are fairly presented, and the bibliography is up to date.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Professor G. Scheltema, 6a Heereplein, Groningen, The Netherlands.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

FOREIGN

Royal Society of Medicine, Section for the Study of Disease in Children

President: R. C. Jewesbury, Esq., M.D., 5 Wimpole St., W. 1, London.
Secretary: Dr. Helen Mackay, 28 John St., W. C. 1, London.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:30 p. m.
Place: Bâle, Switzerland: Time: September, 1935.

NATIONAL

American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. A. Graeme Mitchell, Children's Hospital, Cincinnati.
Secretary: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Place: Atlantic City, N. J. Time: June 10-14, 1935.

American Academy of Pediatrics

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Place: New York. Time: June 7-8, 1935.
Region I. Place: Philadelphia. Time: Fall, 1935.
Regions II and III. Place: St. Louis. Time: Fall, 1935.
Region IV. Place: Seattle. Time: Fall, 1935.

American Child Health Association

President: Dr. Samuel McC. Hamill, 1822 Spruce St., Philadelphia.
Secretary: Dr. Philip Van Ingen, 125 E. 71st., New York.

American Hospital Association, Children's Hospital Section

President: Mr. Robert Witham, Children's Hospital, Denver.
Secretary: Miss Agnes O'Roke, Kosair Crippled Children's Hospital, Louisville, Ky.

American Pediatric Society

President: Dr. Borden S. Veeder, 3720 Washington Ave., St. Louis.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.
Place: Wade Park Manor, Cleveland. Time: May 2-4, 1935.

Canadian Society for the Study of Diseases of Children

President: Dr. D. P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary-Treasurer: Dr. R. R. Struthers, 1414 Drummond St., Montreal.
Place: Buffalo, N. Y. Time: June 1935.

Society of Pediatric Research

President: Dr. Joseph Stokes Jr., Children's Hospital, Philadelphia.
Secretary: Dr. A. A. Weech, Babies Hospital, New York.
Place: Atlantic City, N. J. Time: May 1935.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

SECTIONAL

North Pacific Pediatric Society

President: Dr. Armin Rembe, Stimson Bldg., Seattle.
Secretary: Dr. Frank H. Douglass, 1227 Medical and Dental Bldg., Seattle.

Southern Medical Association, Section on Pediatrics

Chairman: Dr. Oliver W. Hill, 301 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. Madison Hines Roberts, 104 Ponce de Leon Ave., N. E., Atlanta, Ga.

STATE

Alabama Pediatric Society

President: Dr. Charles Abbott, 1817 Broad St., Tusaloosa.
Secretary-Treasurer: Dr. Wallace Clyde, Employee's Hospital, Fairfield.
Place: Mobile. Time: April 17-19, 1935.

Georgia Pediatric Society

President: Dr. Benjamin Bashinski, 700 Spring St., Macon.
Secretary-Treasurer: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.
Place: Atlanta. Time: Dec. 13, 1934.

Louisiana State Pediatric Society

President: Dr. John Signorelli, 2000 Tulane Ave., New Orleans.
Secretary-Treasurer: Dr. Edwin A. Socola, 1027 Canal Bank Bldg., New Orleans.
Place: New Orleans. Time: April 29, 1935.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. George Sincerbeaux, 6 William St., Auburn.
Secretary: Dr. John D. Craig, 12 E. 11th St., New York.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Edgar E. Martmer, 749 David Whitney Bldg., Detroit.
Secretary: Dr. C. R. Dengler, 131 W. Michigan Ave., Jackson.
Place: Flint. Time: September 1935.

Mississippi State Pediatric Society

President: Dr. N. C. Womack, Jackson Infirmary, Jackson.
Secretary-Treasurer: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Place: To be designated by Society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. J. A. Henske, 1614 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. J. H. Murphy, 915 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Second Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. J. Buren Sidbury, 15 N. Fifth St., Wilmington.
Secretary: Dr. E. K. McLean, 121 W. Seventh St., Charlotte.
Place: Various children's hospitals. Time: Twice a year.

Oklahoma State Pediatric Society

President: Dr. C. V. Rice, 222 Wall St., Muskogee.
Secretary: Dr. B. H. Nicholson, 301 N. W. Twelfth St., Oklahoma City.
Place: Oklahoma City. Time: May 1935.

Pennsylvania Medical Society, Pediatric Section

Chairman: Dr. Francis T. O'Donnell, 345 North Main St., Wilkes-Barre.
Secretary: Dr. Theodore O. Elterich, 119 S. Highland Ave., Pittsburgh.
Place: Harrisburg. Time: Sept. 30-Oct. 3, 1935.

South Carolina Pediatric Society

President: Dr. Julian P. Price, Medical Bldg., Florence.
Secretary-Treasurer: Dr. Leland B. Salters, 317 S. Warley Ave., Florence.
Place: Columbia. Time: January 1935.

Tennessee State Pediatric Society

President: Dr. Arthur G. Jacobs, 1193 Madison Ave., Memphis.
Secretary: Dr. Joe T. Smith, 702 Medical Arts Bldg., Knoxville.
Place: Nashville. Time: April 1935.

Texas Pediatric Society

President: Dr. Ramsay H. Moore, 3600 Fairmount St., Dallas.
Secretary-Treasurer: Dr. F. H. Lancaster, Medical Arts Bldg., Houston.

Virginia Pediatric Society

President: Dr. W. P. McDowell, 142 W. York St., Norfolk.
Secretary: Dr. W. A. McGee, 616 W. Grace St., Richmond.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. R. C. Hood, 428 W. Pike St., Clarksburg.
Secretary: Dr. Russell C. Bond, 1325 Chapline St., Wheeling.

LOCAL

Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harry M. Greenwald, 499 Ocean Ave., Brooklyn.
Secretary: Dr. Sylvan D. Lazarus, 847 Lincoln Place, Brooklyn.
Place: Medical Society of County of Kings Bldg., 1313 Bedford Ave., Brooklyn.
Time: Third Wednesday of each month from October to May, 8:30 p. m.

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. A. Garvin, Carnegie Medical Bldg., Cleveland.
Secretary: Dr. William M. Champion, 2323 Prospect Ave., Cleveland.
Place: Cleveland Medical Library Bldg., Time: October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. C. V. Mulligan, 17 Walmer Rd., N., Toronto.
Secretary: Dr. T. B. Verner, 170 St. George St., Toronto.

Bronx Pediatric Society

President: Dr. Morris Gleich, 9 Post Ave., New York.
Secretary: Dr. Harry D. Pasachoff, 1560 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

Chicago Pediatric Society

President: Dr. Stanley Gibson, 9503 Prospect Ave., Chicago.
Secretary: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Place: John B. Murphy Memorial Bldg. Time: Third Tuesday of each month.

Dallas County Pediatric Society

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas, Texas.
Secretary: Dr. R. S. Usry, 1835 Garrett Ave., Dallas, Texas.
Place: Bradford Memorial Hospital. Time: 1 p. m., first and third Saturdays of each month.

Detroit Pediatric Society

President: Dr. Earl W. May, 1551 Woodward Ave., Detroit.
Secretary: Dr. E. A. Wishropp, 10 Peterboro Ave., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Joseph Yampolsky, 478 Peachtree St., Atlanta.
Secretary: Dr. T. I. Willingham, 384 Peachtree St., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Frank Lancaster, Medical Arts Bldg., Houston, Texas.
Secretary-Treasurer: Dr. A. A. Little Jr., 817 Holman Ave., Houston, Texas.
Place: Houston Club: Time: Third Monday of each month.

Intermountain Pediatric Society

President: Dr. Helmina Jeidell, 11 Exchange Pl., Salt Lake City, Utah.
Secretary-Treasurer: Dr. Edwin R. Murphy, 9 Exchange Pl., Salt Lake City, Utah.
Place: Salt Lake City, General Hospital. Time: First Thursday of each month, 8 p. m.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1103 Grand Ave., Kansas City.
Secretary: Dr. S. A. Stadler, 6133 Brookside Blvd., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Henry A. Reisman, 148, 88th Ave., Jamaica, L. I.
Secretary-Treasurer: Dr. Edith A. Mittell, 112 Queens Blvd., Forest Hills, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Clyde V. Croswell, 1052 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month, except June, July and August, 8 p. m.

Milwaukee Pediatric Society

President: Dr. F. R. Janney, 1411 Wauwatosa Ave., Wauwatosa, Wis.
Secretary: Dr. John H. Reynolds, 1628 Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New England Pediatric Society

President: Dr. James L. Gamble, 300 Longwood Ave., Boston.
Secretary: Dr. Gerald Hoeffel, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Harry Bakwin, 132 E. 71st St., New York.
Secretary: Dr. Alexander T. Martin, 107 E. 85th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. O. W. Rowe, 205 W. 2nd St., Duluth, Minn.
Secretary: Dr. E. F. Robb, 1801 Lyndale Ave., S. Minneapolis.
Place: Minneapolis. Time: Spring, 1935.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala, Pa.
Secretary: Dr. James E. Bowman, 4091 Comly St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Carl K. Wagener, Jenkins Arcade, Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200 Fifth Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Tuesday, alternate months from October to April, inclusive.

RICHMOND PEDIATRIC SOCIETY

President: Dr. W. A. McGee, 616 W. Grace St., Richmond, Va.
Secretary-Treasurer: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month (except July, August and September).

ROCHESTER PEDIATRIC SOCIETY

President: Dr. H. F. Rowley, 176 S. Goodman St., Rochester, N. Y.
Secretary: Dr. J. M. Parker, 26 S. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Arthur L. Esserman, Republic Bldg., Denver.
Secretary: Dr. Ralph Verploeg, 19th and Gilpin Sts., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. J. V. Cooke, St. Louis Children's Hospital, St. Louis.
Secretary-Treasurer: Dr. Katherine Bain, Beaumont Bldg., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Armin C. Rembe, Stimson Bldg., Seattle.
Secretary: Dr. Frank H. Douglass, Medical-Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Victor E. Stork, 1136 W. Sixth St., Los Angeles.
Secretary: Dr. Howard R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. John F. Sanders, 320 Townsend St., Lansing, Mich.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.

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